

**Vascepa[®] (icosapent ethyl)
For
Treatment of Hypertriglyceridemia**

**BRIEFING DOCUMENT FOR THE ENDOCRINOLOGIC
AND METABOLIC DRUGS ADVISORY COMMITTEE**

MEETING DATE: 16 October 2013

AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Term
ADR	adverse drug reaction
AHA	American Heart Association
ALA	alpha-linolenic acid
ANCOVA	analysis of covariance
Apo	apolipoprotein
Apo B	apolipoprotein B
BMI	body mass index
CHD	coronary heart disease
CM	chylomicron
CNS	central nervous system
CV	cardiovascular
CVD	cardiovascular disease
DB	double-blind
DHA	docosahexaenoic acid
DGLA	dihomo- γ -linolenic acid;
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FPG	fasting plasma glucose
HbA1c	hemoglobin A1c
HDL-C	high density lipoprotein-cholesterol
HR	hazard ratio
HPA	heneicosapentaenoic acid
hsCRP	high sensitivity c-reactive protein
ISS	integrated summary of safety
ITT	intent-to-treat
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
LDL-C	low density lipoprotein-cholesterol
LLP	light liquid paraffin
LOCF	last observation carried forward
Lp-PLA ₂	lipoprotein-associated phospholipase A2
MI	myocardial infarction
NCEP	National Cholesterol Education Program
NDA	new drug application
NLA	National Lipid Association
Non-HDL-C	non-high density lipoprotein-cholesterol
OM3	(prescription) omega 3 fatty acids
ox-LDL	oxidized low density lipoprotein
PC	placebo-controlled
RLP-C	remnant-like particle cholesterol
SAE	serious adverse event
SD	standard deviation
SDA	Stearidonic acid
SPA	Special Protocol Assessment agreement

TC	total cholesterol
TEAE	treatment emergent adverse event
TG	triglyceride
VLDL-C	very low density lipoprotein cholesterol

1. Executive Summary

The *Endocrinologic and Metabolic Drugs Advisory Committee* has been asked to review the benefit/risk profile of Vascepa[®], a highly purified formulation of ethyl eicosapentaenoic acid (EPA). The FDA approved the New Drug Application (NDA) for Vascepa 4 g/day on 26 July 2012 as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Amarin Pharmaceuticals Ireland Limited (Amarin) submitted a supplemental NDA to the FDA on 21 February 2013 seeking approval of Vascepa for treatment of elevated (200 to 499 mg/dL) TG in patients with mixed dyslipidemia. The proposed indication is as follows:

Vascepa (icosapent ethyl) is indicated as an adjunct to diet and exercise and in combination with a statin to reduce triglyceride TG, non-HDL-C, ApoB, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent.

This document provides a summary of clinical data supporting the benefit-risk profile for Vascepa in this patient population.

1.1 Unmet Medical Need in Treatment of Hypertriglyceridemia

It is well established that low-density lipoprotein cholesterol (LDL-C) is a marker for cardiovascular disease (CVD) risk. Since 1976, the prevalence of high LDL-C levels in the United States has been on the decline, partially due to an increase in the prevalence of statin therapy and to public efforts to reduce cholesterol intake. Contrary to the trend toward increased utilization of LDL-C lowering drug therapy, in 2009 it was estimated that approximately one in five adults in the United States have TG of 200 mg/dL or higher, but that pharmacotherapy is utilized in less than four percent of this population (Ford 2009, Beltran-Sanchez 2013). In addition, while some success has been achieved in reducing cholesterol intake; increased total caloric intake, increased carbohydrate intake, and decreased physical activity have been factors in observed increases in metabolic syndrome, driven by increases in the prevalence of hypertriglyceridemia (HTG), waist circumference, and high blood pressure (Ford 2009). These metabolic syndrome-related changes are likely to be part of the reason why TG reductions have not mirrored LDL-C reductions.

While statins are the treatment of choice for LDL-C lowering, many patients retain a high cardiovascular (CV) risk despite achieving their recommended LDL-C targets. Based on a series of large statin trials, optimal statin treatment reduces CVD events by 30-40% over five years (Cannon 2007, Cholesterol Treatment Trialists' 2008), meaning many patients treated to LDL-C goal still have residual CVD risk. An important independent contributor to this residual risk is elevated non-high density

lipoprotein cholesterol (non-HDL-C), which is often driven by elevated hepatic TG. A growing body of evidence supports hypertriglyceridemia as an important biomarker and risk factor of CV disease (CVD) (Austin 2000, Austin 1998, Assmann 1996, Sarwar 2007).

Lipoproteins are responsible for systemic transport of fat and cholesterol. Chylomicrons, VLDL (and the remnants of chylomicrons and VLDL, termed remnant lipoprotein cholesterol (RLP-C)), IDL, and LDL are considered atherogenic particles since they can deliver cholesterol to peripheral tissues, including the arterial wall. Each of these atherogenic particles carries one apolipoprotein B (apoB) molecule. Conversely, HDL particles carry apolipoprotein A (apoA) and work to remove cholesterol from peripheral tissues and return it to the liver, known as reverse cholesterol transport. HDL is therefore considered anti-atherogenic. Total cholesterol is comprised of HDL-C and the cholesterol carried by the atherogenic, apoB-containing lipoproteins, grouped together as non-HDL-C ($\text{non-HDL-C} = \text{TC} - \text{HDL-C}$). Both non-HDL-C and apoB reflect the total atherogenic lipid burden, have been associated with CVD, and are often considered better independent markers of CV risk than LDL-C alone, particularly in statin-treated patients. (Ballantyne 2012). Importantly, in hypertriglyceridemia (HTG) the entire lipid profile is shifted, resulting in a more atherogenic lipid profile; including increased VLDL-C, decreased HDL-C, and decreased LDL-P size, and often includes increased LDL-P number. The increased cholesterol carried by TG-rich lipoproteins (e.g. VLDL-C, IDL-C, and RLP-C) in HTG drives an increase in non-HDL-C.

These interdependent, physiologic relationships of TG, cholesterol, and the lipoproteins that carry them explain the long-standing association between HTG and CVD. While it has been established that high TG is associated with CVD, what has been under debate is whether TG represents an independent risk factor for CVD. The tight interplay between TG and other lipid parameters has resulted in the predictive value of TG to be attenuated when risk models are corrected for these parameters, such as non-HDL-C, HDL-C, or ApoB. Due to the complex biological interdependence between TG, cholesterol, and the lipoproteins that carry them, it is challenging to design appropriate adjustments to risk models that accurately reflect physiological connections between lipids. In other words, the attenuation of TG as an independent CV risk factor would be expected when a model adjusts for tightly correlated lipids such as HDL-C or non-HDL-C. Despite the struggle to design appropriate risk models to test TG as an independent CV risk factor, TG continues to be regarded as an important biomarker of CVD based on its association with an atherogenic lipid profile. In addition, non-HDL-C has been demonstrated to be an independent risk factor for CVD, and high hepatic TG levels are an important factor in the elevation non-HDL-C. Finally, the need to treat elevated non-HDL-C is reflected in the residual CV risk observed in patients with optimized LDL-C.

The importance of elevated non-HDL-C in HTG is reflected in the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) where non-HDL-C was added as a secondary target of therapy (Grundy 2004). After diet and lifestyle modification, and after reaching LDL-C goal, if a patient has persistently elevated TG (≥ 200 mg/dL) ATP III recommends a secondary treatment goal for non-HDL-C. Because high levels of hepatic TG are a driver of non-HDL-C, TG-lowering therapies added to statin therapy are key therapeutic options for the reduction of non-HDL-C with maintenance of LDL-C reduction.

Beyond ATP III, many additional expert panels and professional organizations also recognize the association of increased TG levels with CV risk. The American Heart Association (Miller 2011), American Diabetes Association, American College of Cardiology (Brunzell 2008), American Association of Clinical Endocrinology (Jellinger 2012) and The Endocrine Society (Berglund 2012) all recommend or support the lowering non-HDL-C through TG reduction once optimal LDL-C levels have been reached. For many patients non-HDL-C can be reduced with diet and lifestyle modification. However many will require cholesterol-lowering medication (e.g. increasing statin therapy) or TG-lowering therapies.

Limitations of current therapies may be partially responsible for the high rate of discontinuation of some lipid altering therapies within the first 18 months (Abughosh 2004), which may limit their ability to provide long-term CV benefit. Fibrates, the prescription omega acid mixture (Lovaza[®]), dietary supplements containing omega acid mixtures, and other marine oils, can all increase LDL-C (Jacobson 2012). Both fibrates and niacin may increase the risk for myopathy as monotherapy, and this risk is increased when combined with statins. Additional safety concerns include contraindications in liver disease (fibrates and niacin) and gallbladder or renal disease (fibrates) (Trilipix PI 2012). Niacin may also worsen glycemic control in diabetic patients and cause flushing that may interfere with compliance and lead to premature discontinuation of treatment (Niaspan PI 2013). A new treatment for patients with high TG (200 to 499 mg/dL) that can safely and effectively lower TG, VLDL-C, non-HDL-C, while not perturbing LDL-C regulation by a statin, would be desirable to address the limitations of current therapy and to provide clinicians an additional treatment option to consider as an add-on to optimized statin therapy.

1.2 Vascepa Clinical Development Program

Vascepa contains the single omega-3 fatty acid EPA, and is the sole prescription omega acid product approved in the United States that contains only EPA.

The Vascepa clinical development program was comprised of three randomized, placebo-controlled, Phase 3 studies in hypertriglyceridemia; two pharmacokinetic

studies conducted in healthy subjects; three drug interaction studies; and eight studies in CNS development (e.g., Huntington's disease).

Regarding Vascepa pharmacokinetics; EPA ethyl ester is absorbed at the small intestine, assembled into TG, incorporated into chylomicrons, and released into systemic circulation, similar to other long-chain fatty acids. Once in the plasma, EPA can be delivered to tissues throughout the body for various uses, including energy (β -oxidation) and incorporation into complex lipids in circulation and cellular membranes. β -oxidation can occur in almost all tissues (notably not in the brain) and is the primary route of EPA metabolism (Ishiguro 1988b, Frøyland 1997, Du 2010). Cytochrome P450- and cyclooxygenase/lipoxygenase (COX/LOX)-mediated pathways are only minor contributors to the metabolism and elimination of EPA (Konkel 2011). Despite cytochrome P450 providing a minor route of EPA metabolism, possible drug interactions were investigated by Amarin. In human microsomes, EPA was found to be a weak inhibitor of some Cytochrome P450 (CYP) isoforms, and these isoforms were then studied in clinical drug-drug interaction studies. EPA demonstrated no clinically significant effect on the pharmacokinetics of omeprazole (CYP2C19), rosiglitazone (CYP2C8), warfarin (CYP2C9), or atorvastatin (CYP3A4).

The three Phase 3, randomized, double-blind, placebo-controlled trials in the CV clinical development program for Vascepa are listed in Table 1. MARINE was conducted in patients with severe HTG (≥ 500 mg/dL) and led to initial FDA approval. ANCHOR was conducted in patients at high risk for CVD who had well controlled LDL-C through statin therapy, but persistently elevated TG (200 to 499 mg/dL). The results from ANCHOR are the subject of this advisory committee meeting. As agreed with the FDA, Amarin is currently sponsoring a large, randomized, double-blind, placebo-controlled CV endpoint study (REDUCE-IT). Similar to ANCHOR, patients in REDUCE-IT are a high CV risk population, that have well controlled LDL-C via statin management, but continue to have elevated TG.

Table 1: Randomized Placebo-Controlled Phase 3 Vascepa Studies in Hypertriglyceridemia

	ANCHOR (AMR-01-01-0017)	MARINE (AMR-01-01-0016)	REDUCE-IT (AMR-01-01-0019)
Patient population	Mixed dyslipidemia on statin therapy, and at high risk for CVD (200-499 mg/dL TG)	Hypertriglyceridemia (≥ 500 mg/dL TG)	Mixed dyslipidemia on statin therapy, and at high risk for CVD (200-499 mg/dL TG)
Primary Endpoint	TG reduction	TG reduction	Reduction in CV events
Study Design	12-Week DB, PC	12-Week DB, PC	DB, PC outcome study over ~4 years
Dose	2 and 4 g/day Vascepa, placebo	2 and 4 g/day Vascepa, placebo	4 g/day Vascepa
Statin Use	All patients	~25% of patients	All patients
Number of Patients	702	229	~8000
Geographic Location	US only	Global	Global
Status	Completed	Approval for indicated population is based on this completed study	Ongoing

ANCHOR Regulatory History

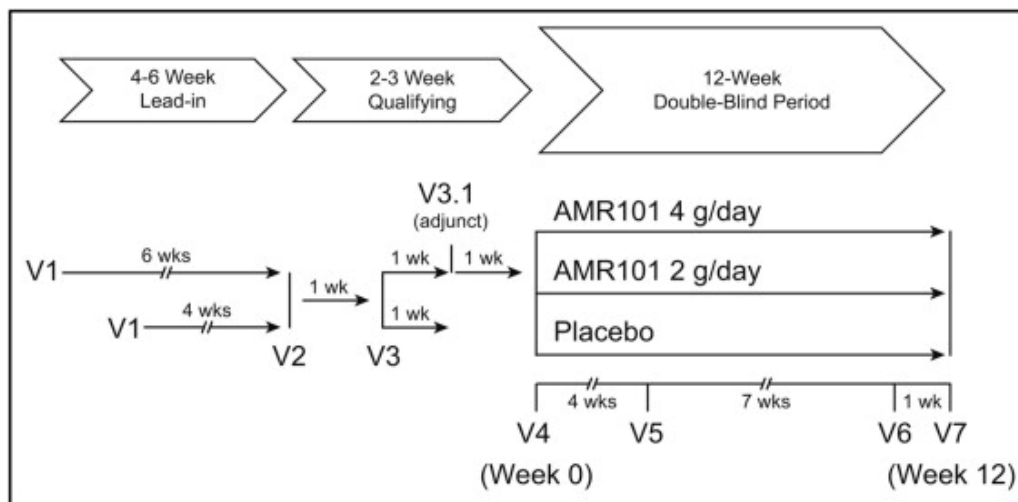
Development of the MARINE, ANCHOR and REDUCE-IT protocols reflect significant input from the FDA at a pre-IND meeting and through a Special Protocol Assessment (SPA) review and discussion for each protocol subsequently resulting in a SPA agreement for each. Some key parameters of these agreements for ANCHOR included 1) use of a 2 g/day and 4 g/day dose of Vascepa, 2) study endpoints including primary efficacy analysis (placebo-adjusted percent change in TG from baseline to Week 12) and a pre-specified analysis to show non-inferiority of Vascepa compared to placebo in the Week 12 change from baseline for LDL-C, 3) important conduct elements, such as statin dosing optimized during run-in such that LDL-C was at goal prior to randomization, and 4) choice of light liquid paraffin oil (LLP) as the placebo comparator.

ANCHOR Study Design

ANCHOR was a randomized, double-blind, placebo-controlled Phase 3 study conducted at 97 sites in the United States. The target population included patients at high risk for CVD (defined by ATP III) that, despite statin treatment to achieve reasonably controlled LDL-C (≥ 40 to < 100 mg/dL [revised to ≥ 40 to < 115 mg/dL

via an amendment]), still presented with persistently high fasting TG levels (200 to < 500 mg/dL [revised to 185 to <500 mg/dL with via an amendment]). Patients entered a four to six week diet/lifestyle, lipid medication washout, and statin stabilization (for statin naïve patients) period and then entered a two week TG and LDL-C qualifying period, followed by randomization into a double blind placebo-controlled treatment period. A total of 702 patients meeting eligibility criteria were randomized to Vascepa 4 g/day (n = 233), Vascepa 2 g/day (n = 236), or placebo capsules (n = 233) (Figure 1).

Figure 1: ANCHOR Study Design



Key exclusion criteria for ANCHOR included body mass index (BMI) >45 kg/m², hemoglobin A1c (HbA1c) >9.0% (revised to >9.5% via an amendment) at screening, use of any non-study, drug-related, non-statin, lipid-altering medications or supplements (e.g. niacin >200 mg daily, fibrates, omega acid mixture medications or supplements), percutaneous coronary intervention within 4 weeks prior to screening, and hospitalization for acute coronary syndrome and discharge within 4 weeks prior to screening. Eligible patients were required to be on a stable statin therapy (≥4 weeks prior to the TG qualifying period; with or without ezetimibe). This statin therapy was required to be atorvastatin, rosuvastatin, or simvastatin, have been optimal (LDL-C control as described above ≥40 mg/dL and ≤115 mg/dL), and continued at the same dose until the end of the study.

Choice of Placebo

Corn oil, which had been used as a placebo in other trials of omega 3 polyunsaturated fatty acids, contains triglycerides and has a distinctive yellow color different from

icosapent ethyl (colorless). Therefore, Amarin proposed to use light mineral oil, NF, in the placebo capsules for the pivotal studies. The FDA agreed that light mineral oil was acceptable as a placebo as long as the amount per capsule did not exceed the amounts in FDA-approved products given by the same route of administration. Each placebo capsule contained approximately 1 g of light mineral oil, which was dosed two capsules twice daily with food, or about 4 mL/day. Mineral oil has been medically used as a laxative at much higher doses of 15 – 45 mL/day.

Light mineral oil, also known as light liquid paraffin (LLP), is highly refined mineral white oil and is a mixture of liquid hydrocarbons obtained from petroleum, which do not contain any functional groups (e.g., no carboxyl groups in contrast with fatty acids in vegetable oils) and are considered chemically inert with minimal systemic absorption.

Paraffin oil is listed as “generally recognized as safe” in the United States. (US Food and Drug Administration. GRAS Notice Inventory. GRN No. 71: 2012). White mineral oil is also permitted for direct addition to food for human consumption. Paraffin oil is listed as “generally recognized as safe” in the United States. (21 CFR 172.878 2013)

Paraffin oil has been used as placebo in clinical studies and has a documented lack of effect on lipids such as triglycerides, LDL-C, and fatty acids (DeTruchis 2007, Kabir 2007, McDaniel 2010, Horrobin 1991). In the ANCHOR study (as well as the MARINE and REDUCE-IT studies), the amount of LLP used in each placebo capsule was approximately 1 mL (matched with Vascepa for equal fill volume). The total daily dose of LLP was 2 to 4 capsules, which was administered as 2 capsules/day (2 mL/day) of LLP in the Vascepa 2 g/day arm, or 4 capsules/day (4 mL/day) in the control arm.

Although isolated earlier publications suggested that mineral oil may interfere with the absorption of fat-soluble substances, more recent reports (Sharif 2001, and Gal-Ezar 2006) concluded that mineral oil induced fat-soluble vitamin deficiency is unfounded, indicating that this is not expected at the low doses used in ANCHOR.

Overall, LLP was chosen as placebo because it is chemically inert, has minimal absorption, does not alter lipids, is well matched with Vascepa for color, is safe, and does not interfere with the absorption of fat soluble vitamins at the doses used in the ANCHOR study. There is no scientific evidence that trends for increase in lipid parameters in the placebo arm in the at-risk patient population that was studied in ANCHOR were caused by the placebo and, as described herein, Vascepa’s overall results were favourable both on a placebo corrected and non-placebo corrected basis.

Statistical Methodology

The statistical methodology used in ANCHOR included a sample size estimation that was dictated by the prespecified noninferiority comparison of percent change from baseline in LDL-C. A sample size of 194 completed patients per treatment arm was to provide 80% power to demonstrate non-inferiority ($p < 0.025$, one-sided) of the LDL-C response between Vascepa 4 g/day and placebo, within a 6% margin (which corresponds with the approximate reduction in LDL-C observed with doubling the dose of a statin). To accommodate an approximate 10% drop-out rate from randomization to completion of the double-blind treatment period, a total of 648 randomized patients was planned (216 patients per treatment arm). A 15% difference between Vascepa 4 g/day and placebo was the treatment effect of interest for TG percent change from baseline. Based upon the 194 patients per treatment arm needed for the noninferiority comparison, and assuming a standard deviation of 45% in TG measurements, 194 patients per treatment arm would provide 90.6% power to detect a clinically meaningful 15% difference (testing at 0.05 significance level). For all primary and secondary endpoints, Week 12 percent change from baseline was calculated for each patient. The method of analysis for the primary and secondary endpoints was prespecified as either an analysis of covariance (ANCOVA) model if the data for that endpoint were normally distributed or a Wilcoxon-rank-sum test if the data were not normally distributed. Significant departure from normality was defined as p-value of < 0.01 for the Shapiro-Wilk test and/or homogeneity of variance. All primary and secondary endpoints were non-normal in distribution dictating analysis by Wilcoxon-rank-sum testing.

Patients were stratified by type of statin (atorvastatin, rosuvastatin, or simvastatin), the presence of diabetes, and gender.

Endpoints

Dose-dependent effects were observed in many endpoints with Vascepa 2g/day and 4g/day, and overall study protection against false positive findings (alpha) was implemented across dose comparisons. While we will report results from both doses in this Briefing Book, our discussion will primarily focus on the 4 g/day dose, as 4 g/day provides a good balance of safety and efficacy.

The primary endpoint in ANCHOR was a change in TG from baseline to Week 12 as compared to placebo. Because some treatments to lower TG can increase LDL-C, it was also planned to simultaneously demonstrate that Vascepa did not lead to a material increase in LDL-C through a non-inferiority test with a +6 percentage point margin, defining an outcome consistent with inferiority. The criterion for rejecting the null hypothesis that inferiority exists (concluding evidence of non-inferiority) is that the

upper limit of one-sided 97.5% confidence interval be less than +6 percentage points. The +6 percentage point margin came from a consideration of 6% being the approximate effect size on LDL-C of doubling a statin dose.

The secondary efficacy endpoints were conditional on meeting criterion for both primary endpoints and were controlled for multiplicity. These secondary endpoints included the percent changes from baseline to Week 12, compared to placebo, in LDL-C, non-HDL-C, VLDL-C, lipoprotein-associated phospholipase A2 (Lp-PLA₂) and apolipoprotein B (Apo B). High density lipoprotein cholesterol (HDL-C), VLDL-TG, high-sensitivity C-reactive protein (hsCRP), oxidized LDL (ox-LDL), and RLP-C were included as exploratory endpoints.

Safety assessments in ANCHOR included adverse events, clinical laboratory measurements (chemistry, haematology, and urinalysis), 12-lead electrocardiograms (ECGs), weight and BMI, vital signs, and physical examinations.

Clinical Efficacy

Overall, 702 patients were randomized to Vascepa 4 g/day, Vascepa 2 g/day, or placebo. Study completion rates were high in all three treatment arms with reasons for discontinuation well balanced between arms. The demographic, baseline statin, and baseline laboratory characteristics were well balanced between treatment arms. Across the three treatment arms, the mean age was 61.4 years and the mean BMI was 32.9 kg/m², with over half of the patients being obese. Approximately 73% of patients in each treatment arm in ANCHOR had diabetes (one patient had Type 1, all others had Type 2), with 20.8% having diabetes and CVD, and 83% had a baseline diagnosis of hypertension; these characteristics were similar across treatment arms. Simvastatin was the most common statin used in all arms. TG and LDL-C levels were well balanced within the statin efficacy regimens (low, medium and high potency).

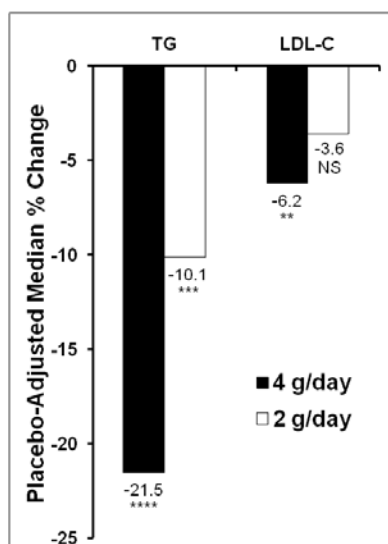
Primary Endpoints

As presented here and in peer-reviewed publications (Ballantyne 2012; Brinton 2013), both doses of Vascepa met the pre-specified criteria to confirm a beneficial reduction in TG compared to placebo (Figure 2 and Table 2). The placebo corrected change from baseline at the 12 week endpoint was –21.5 percentage points ($p < 0.0001$) for 4 g/day and –10.1 percentage points ($p = 0.0005$) for 2 g/day. Within this Briefing Book, percent changes for Vascepa compared to placebo arms are presented as differences in percentage points, and are sometimes simply referred to as percent changes. The difference from placebo was observable at 4 weeks and sustained at 12 weeks. Sensitivity analyses and analyses by patient subgroups support the robustness and consistency of the primary TG analysis. In addition, a post-hoc analysis conducted to

examine the impact of the protocol amendment (which modified inclusion criteria for TG and LDL-C) found the TG results for both Vascepa 4 g/day and Vascepa 2 g/day prior to and after the FDA-agreed amendment were similar.

The non-inferiority assessment for LDL-C increase met the statistical criterion for non-inferiority. The median percent change in LDL-C at Week 12 was lower by 6.2 percentage points in the Vascepa 4g/day arm relative to the placebo arm (Figure 2). Median percent change from baseline to end of treatment for LDL-C was 1.5% for the Vascepa 4 g/day, 2.4% for the Vascepa 2 g/day, and 8.8% for the placebo. For Vascepa 4 and 2 g/day, the upper limit of the 97.5% confidence interval for the difference from placebo was less than +6 percentage points (–1.7 percentage points and +0.5 percentage points, respectively), indicating both doses were non-inferior to placebo based upon the protocol specified analysis.

Figure 2: Placebo-Adjusted Median Percentage Point Changes in TG and LDL-C in ANCHOR



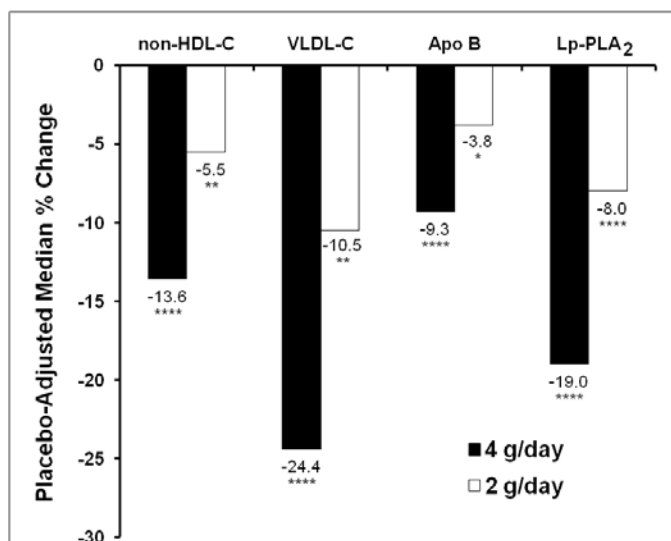
**** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; NS = Not Significant (p≥0.05)

Secondary and Exploratory Endpoints

The lipid and lipoprotein endpoint non-HDL-C, VLDL-C, and Apo B, as well as inflammatory marker LpPLA₂, were significantly decreased in patients treated with 4 g/day Vascepa compared to placebo (Figure 3). Both 2 and 4 g/day Vascepa were associated with a small decrease in HDL-C (Table 2). The exploratory endpoints of hsCRP, ox-LDL, and RLP-C were also significantly changed with Vascepa 4 g/day compared to placebo (Figure 4), as were TC, VLDL-TG (Table 2), as were apo A-1 (–

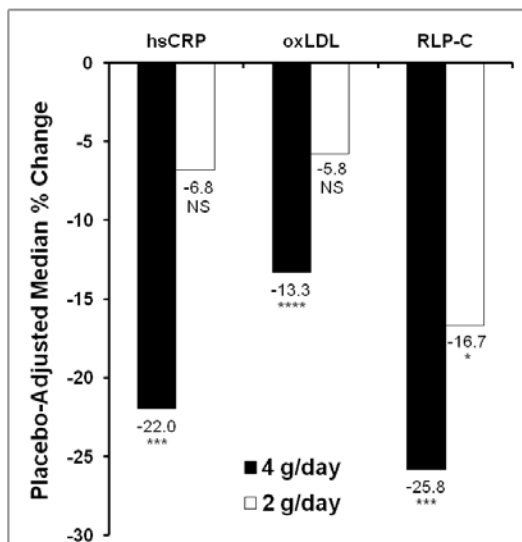
2.9 percentage points, $p < 0.0001$), and LDL-P concentration and size (Ballantyne 2013). Total LDL-P concentration decreased 7.7 percentage points with Vascepa 4 g/day versus placebo ($p = 0.0017$) and decreased 7.5 percentage points for 2 g/day Vascepa versus placebo ($p = 0.0013$), which was driven by decreases in small LDL-P concentrations (−13.5 percentage points for Vascepa 4g/day ($p < 0.0001$) and −14.7 percentage points for Vascepa 2 g/day ($p < 0.0001$), both compared to placebo). LDL-P size increased with Vascepa 4 g/day (+0.5, $p = 0.0031$) and 2 g/day (+0.5, $p = 0.0007$) compared to placebo. No differences between Vascepa and placebo were observed in other lipids and markers of inflammation, such as intercellular adhesion molecule 1 (ICAM-1) and interleukin-6 (IL-6) (Bays 2013), or plasminogen activator inhibitor-1 (PAI-1) and lipoprotein(a) (Lp(a), data not shown).

Figure 3: Placebo-Adjusted Median Percentage Point Changes in Secondary Endpoints in ANCHOR



**** $p < 0.0001$; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; NS = Not Significant ($p \geq 0.05$)

Figure 4: Placebo-Adjusted Median Percentage Point Changes in Exploratory Endpoints in ANCHOR



**** $p < 0.0001$; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; NS = Not Significant ($p \geq 0.05$)

Table 2. Changes in Efficacy Endpoints in ANCHOR from Baseline to Week 12

Endpoint (n=4 g/day, 2 g/day, placebo)	Vascepa 4 g/day (n = 226)			Vascepa 2 g/day (n = 234)			Placebo (n = 227)			Median Placebo- adjusted Change from Baseline	
	Baseline	End-of-Treatment	Change from Baseline (%)	Baseline	End-of-Treatment	Change from Baseline (%)	Baseline	End-of-Treatment	Change From Baseline (%)	Vascepa 4 g/day vs Placebo (%; p Value)	Vascepa 2 g/day vs Placebo (%; p Value)
Primary End Point											
Triglycerides (mg/dL) (n = 226, 234, 227)	264.8 (93.0)	220.8 (92.0)	-17.5 (31.0)	254.0 (92.5)	244.3 (117.0)	-5.6 (34.5)	259.0 (81.0)	269.5 (149.5)	5.9 (44.9)	-21.5 <0.0001	-10.1 0.0005
Secondary End Points											
Low-density lipoprotein cholesterol* (mg/dL) (n = 225, 233, 226)	82.0 (25.0)	83.0 (31.0)	1.5 (26.6)	82.0 (24.0)	87.0 (27.0)	2.4 (26.1)	84.0 (27.0)	88.5 (31.0)	8.8 (31.0)	-6.2 0.0067	-3.6 0.0867
Non-high-density lipoprotein cholesterol (mg/dL) (n = 226, 234, 227)	128.0 (32.0)	122.0 (39.0)	-5.0 (21.3)	128.0 (33.0)	134.0 (41.0)	2.4 (26.1)	128.0 (34.0)	138.0 (43.0)	9.8 (27.6)	-13.6 <0.0001	-5.5 0.0054
Very low-density lipoprotein cholesterol (mg/dL) (n = 225, 233, 226)	44.0 (21.0)	38.0 (22.0)	-12.1 (47.9)	43.0 (21.0)	44.0 (25.0)	1.6 (54.6)	42.0 (21.0)	49.0 (28.0)	15.0 (58.8)	-24.4 <0.0001	-10.5 0.0093
Lipoprotein-associated phospholipase A ₂ (ng/ml) (n = 217, 224, 213)	180.0 (56.0)	160.0 (57.0)	-12.8 (18.5)	190.0 (55.5)	183.5 (57.5)	-1.8 (23.1)	185.0 (58.0)	200.0 (71.0)	6.7 (24.0)	-19.0 <0.0001	-8.0 <0.0001
Apolipoprotein B (mg/dL) (n = 217, 227, 219)	93.0 (23.0)	90.0 (25.0)	-2.2 (16.4)	91.0 (22.0)	95.0 (24.0)	1.6 (20.7)	91.0 (24.0)	98.0 (25.0)	7.1 (23.2)	-9.3 <0.0001	-3.8 0.0170
Selected Exploratory End Points											
Total cholesterol (mg/dL) (n = 226, 234, 227)	167.0 (38.0)	162.0 (38.0)	-3.2 (16.8)	169.0 (34.0)	175.0 (44.0)	2.1 (19.6)	168.0 (38.0)	181.0 (46.0)	9.1 (20.8)	-12.0 <0.0001	-4.8 0.0019
High-density lipoprotein cholesterol (mg/dL) (n = 226, 234, 227)	37.0 (12.0)	37.0 (13.0)	-1.0 (18.2)	38.0 (13.0)	38.0 (11.0)	0.0 (19.5)	39.0 (12.0)	40.0 (14.0)	4.8 (22.0)	-4.5 0.0013	-2.2 0.1265
Very-low-density lipoprotein triglycerides (mg/dL) (n = 225, 233, 226)	190.0 (99.0)	147.0 (88.0)	-19.2 (46.2)	185.0 (86.0)	168.0 (98.0)	-2.1 (48.9)	183.0 (94.0)	196.0 (136.0)	8.9 (63.8)	-26.5 <0.0001	-11.3 0.0049
High-sensitivity C-reactive protein (mg/l) (n = 217, 227, 219)	2.2 (2.7)	2.0 (3.0)	-2.4 (62.8)	1.9 (2.9)	2.5 (3.4)	10.3 (88.6)	2.2 (4.0)	2.6 (4.7)	17.1 (108.0)	-22.0 0.0005	-6.8 0.2889

Data presented as median (interquartile range) for endpoint values. *For LDL-C, non-inferiority analysis was a primary endpoint; % change from baseline was secondary.

1.3 Clinical Safety

The Vascepa clinical development program consists of 15 completed studies; two Phase 1 studies in healthy subjects; three drug interaction studies, two Phase 3 clinical studies in patients with hypertriglyceridemia, and eight clinical studies in patients with central nervous system (CNS) disorders. The REDUCE-IT study is ongoing.

The safety summary reported in this briefing document focuses on safety data from ANCHOR which was similar to the NDA indication study, MARINE. In ANCHOR, Vascepa was generally well tolerated and safe. The incidence of at least 1 treatment emergent adverse event (TEAE) was similar across treatment arms as was AE severity (classified as mild, moderate or severe). Severe AEs and SAEs occurred at similar incidences in the 4 g/day and placebo arms, but discontinuation with AEs was more likely in the placebo arm than in either the Vascepa 2 or 4 g/day arms. One death was reported in a patient treated with placebo.

In ANCHOR, AEs were generally similar across treatment arms. AEs occurring at $\geq 1\%$ incidence and numerically greater in the 4 g arm compared to placebo were arthralgia (1.7%), dizziness (1.7%), fatigue (1.7%), gastroesophageal reflux disease (1.3%), pain in extremity (1.3%), peripheral edema (1.3%), and upper respiratory tract infection (2.6%).

The overall SAE incidence was similar across treatment arms. In the Vascepa 4 g arm, 3.0% of patients had at least 1 SAE compared to 2.5% in the Vascepa 2 g arm and 2.1% in placebo. There was little difference between arms for each specific SAE

In post-marketing safety surveillance, Vascepa remains well-tolerated with no serious adverse drug experiences and with the most commonly reported experiences associated with gastrointestinal disorders (abdominal discomfort and diarrhea).

Prior studies using omega acid mixtures have reported adverse events of interest such as bleeding, hepatic disorders and glucose control, which are discussed below.

Adverse Events of Interest

Incidence of Bleeding

In ANCHOR the incidence of bleeding-related AEs was low in all treatment arms, but occurred more often on Vascepa 4g/day (2.4%) than on placebo (1.3%). A total of 19 bleeding-related AEs occurring in 17 ANCHOR patients (15 on Vascepa and 4 on placebo). There were 2 cases of CNS bleeding, one occurred in a 72 year old female (patient 010-017) randomized to the Vascepa 2 g/day arm. Twenty-one days after her last dose of Vascepa, she suffered a fall resulting in a traumatic head injury. The

second case was reported in a 49 year old female (patient 019-016) randomized to the Vascepa 4g/day arm. During treatment she had a ruptured anterior communicating artery aneurysm. These cases are discussed in detail in Section 5.

Hepatic Disorders

No clinically significant increases in hepatic laboratory values were reported in ANCHOR. Although five patients in ANCHOR experienced hepatic disorders (characterized by ALT >3x ULN, AST >3x ULN, or CK >5x ULN) during the treatment period, no patients had values of ALT >5x ULN, AST >5x ULN, or values that met the criteria for Hy's Law. None of the five patients experienced elevations of alkaline phosphatase and bilirubin (Section 5).

Glucose Control

Vascepa demonstrated no deleterious effect on glucose control as compared to the placebo arm in ANCHOR, as evidenced by a lack of statistically significant changes with either dose. Post-hoc analysis in the diabetic subgroup (73% of total population) exhibited results similar to the overall study population. There were no statistically significant changes in FPG, HbA1c, insulin or HOMA-IR (Brinton 2013). Although not statistically significant, FPG in the Vascepa 4g/day arm showed a numerically greater increase from baseline to 12 weeks compared to placebo and Vascepa 2 g/day arm. Yet, stronger predictors of glycemic control (HbA1c, fasting plasma insulin, and HOMA-IR), were similar between Vascepa and placebo arms.

Therefore, the totality of the ANCHOR data including change from baseline HbA1c, HOMA-IR, and fasting plasma glucose and fasting plasma insulin suggests that Vascepa is unlikely to significantly alter glucose metabolism. The effect of Vascepa on glucose metabolism is explored in further detail in section 5.

1.4 Benefit Risk Conclusion

Many patients retain a high cardiovascular (CV) risk despite achieving their recommended LDL-C targets. Based on a series of large statin trials, optimal statin treatment reduces CVD events by 30-40% over five years (Cannon 2007, Cholesterol Treatment Trialists' 2008), meaning many patients treated to LDL-C goal still have residual CVD risk. An important independent contributor to this residual risk is elevated non-high density lipoprotein cholesterol (non-HDL-C), which is often driven by elevated hepatic TG. A growing body of evidence supports TG as an important biomarker of CV risk (Austin 2000, Austin 1998, Assmann 1996, Sarwar 2007).

After diet and lifestyle modification, and after reaching LDL-C goal, if a patient has persistently elevated TG (≥ 200 mg/dL), ATP III recommends a secondary treatment goal for non-HDL-C. TG-lowering therapies are key therapeutic options for the reduction of non-HDL-C in this hypertriglyceridemic patient population.

Current TG-lowering therapies, including fibrates, niacin, and omega acid mixtures limitations. These limitations contribute to a high rate of treatment discontinuation within the first year of therapy (Abughosh 2004).

- Increase in LDL-C

Fibrates, the prescription omega acid mixture (Lovaza), dietary supplements containing omega acid mixtures, and other marine oils, can all increase LDL-C (Jacobson 2012).

- Myopathy and Contraindications in Liver Disease

Fibrates and niacin may increase the risk for myopathy as monotherapy and this risk is increased when combined with statins. Fibrates and niacin also include contraindications in liver disease.

- Contraindications in Gallbladder and Renal Disease

Fibrates additionally include contraindications in gallbladder and renal disease.

- Worsening Glycemic Control and Flushing

Niacin may worsen glycemic control in diabetic patients and causes flushing in many patients, which may interfere with compliance and lead to premature discontinuation of treatment (Niaspan PI 2013).

A new treatment for patients with high TG (200 to 499 mg/dL) that can safely and effectively be added on to a statin to lower TG, VLDL-C and non-HDL-C, while not increasing LDL-C is needed.

Vascepa has been shown to be a safe and effective therapy when added to statin therapy to significantly reduce TG, while meeting the FDA-agreed pre-specified non-inferiority assessment for LDL-C. In ANCHOR, the placebo adjusted change in fasting TG from baseline at Week 12 with Vascepa 4 g/day was -21.5 percentage points ($p < 0.0001$). Improvements in other lipid and inflammatory parameters were also demonstrated, including non-HDL-C, LDL-C, VLDL-C, RLP-C, Apo B, Lp-PLA₂, hsCRP, ox-LDL, RLP-C, and LDL-P concentration and size. These results suggest a beneficial effect on a fuller picture of atherogenic risk, including lipid burden and inflammation, both associated with plaque formation and atherosclerosis. The data support the conclusion that Vascepa provides benefits to patients when taken as an adjunct to diet and in combination with a statin for the reduction of TG, non-HDL-C, Apo B, LDL-C, TC, and VLDL-C in patients with mixed dyslipidemia and high risk

for CVD.

Within the clinical studies, Vascepa was well tolerated with a low incidence of reported AEs. Overall, AE incidence was similar to placebo. There were no clinically meaningful changes in laboratory parameters. No statistically significant differences were seen in the efficacy or safety profile in diabetic patients compared to non-diabetic patients. Prior studies using omega acid mixtures have reported adverse events such as bleeding and hepatic disorders. These AEs were reviewed for Vascepa. Within the clinical program, Vascepa demonstrated no clinically meaningful effect on hepatic function. The incidence of bleeding-related AEs in ANCHOR was low in all treatment groups, but occurred more often on Vascepa (2.4%) than on placebo (1.3%). Even though the incidence is greater, it remains substantially low. Currently approved labeling for Vascepa advises physicians that omega-3s may be associated with an increased risk for bleeding. Since approval of the original NDA for severe hypertriglyceridemia, no new safety concerns have emerged.

Vascepa offers advantages over existing TG-lowering therapies. One of key benefits of Vascepa therapy is the absence of a significant increase of LDL-C, since fibrates and omega acid complex mixtures that contain EPA+DHA are known to increase LDL-C levels in hypertriglyceridemic patients (Goldberg 1989, Bays 2008). A further benefit of Vascepa therapy is that it does not interfere with glucose control. While small numerical elevations were seen in FPG, they were not statistically significant or clinically meaningful. The more accurate markers of glucose control (insulin, HbA1c, HOMA-IR) were similar between active and placebo arms.

Patients who are at high risk for CVD who are taking statin therapy and have persistently high TGs are at-risk and need a safe and effective therapy that can be added to their statin therapy for more aggressive and comprehensive lipid control. If approved, Vascepa would fill an important unmet medical need for these patients.

2. Unmet Medical Need in Mixed Dyslipidemia

2.1 Summary

There is an unmet medical need in patients with mixed dyslipidemia as evidenced by the following:

- Risk Reduction
 - LDL-C lowering (through statin or other therapies) effectively addresses some, but not all, CV risk.
 - Non-HDL-C is an independent marker of CV risk and reflects much of the residual CV risk observed once LDL-C is at goal.
 - TG is considered an important biomarker of atherogenic dyslipidemia.
 - TG-reduction is a key therapeutic option for the reduction of non-HDL-C.
 - Reduction in multiple atherogenic lipid parameters – as reflected by LDL-C, VLDL-C, RLP-C, TC, TG, Apo B, and LDL-particle number (LDL-P) – are expected to further reduce CV risk.
 - Reductions in markers of inflammatory responses – such as high sensitivity c-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA₂), and oxidized LDL (ox-LDL) – have been associated with reduced atherogenic plaque progression and vascular function, and therefore may also predict reduced CV risk.
- Treatment Goals
 - Approximately one in five people in the United States have TG \geq 200 mg/dL.
 - Current ATP III and other treatment guidelines factored in data demonstrating that patients at LDL-C goal but with elevated non-HDL-C have residual CV risk.
 - Current guidelines recommend reduction of elevated non-HDL-C when TG \geq 200 mg/dL in patients who have reached target LDL-C.
- TG Lowering Therapies
 - Current treatments for elevated TG have limitations.
 - Fibrates and omega acid mixtures can increase LDL-C in some patients.
 - Fibrates can increase myopathy and are contraindicated in liver, gallbladder, and renal disease.
 - Niacin causes flushing that can lead to treatment discontinuation.
 - Both fibrates and niacin are associated with drug-drug interactions, including in combination with statins.

- There is continuing unmet medical need for an FDA-approved mixed dyslipidemia therapy that is safe and well tolerated and that significantly lowers TG, non-HDL-C, VLDL-C, and Apo B while not perturbing statin control of LDL-C. Vascepa would fulfill this need.

2.2 Hypertriglyceridemia, EPA, and CV Risk

LDL-C has been well established as a marker for CV risk. Since 1976, the prevalence of high LDL-C levels in the United States has been on the decline (from 59% in 1976-1980, progressively decreasing to 27% in 2007-2010; high LDL-C defined as measured LDL-C above the treatment goals established by the National Cholesterol Education Program's Adult Treatment Panel III guidelines), primarily due to public efforts to reduce cholesterol intake and to an increase in the prevalence of statin therapy (less than 1% of population used statins in 1976-1980, progressively increasing to 23% in 2007-2010). Contrary to the trend toward lower LDL-C, TG had continued to rise until about 2005, when decreases began to be observed. (National Center for Health Statistics 2013; Cohen 2010, Harris 1998, Cheung 2009). Despite these very recent decreases in TG, in 2009 it was estimated that approximately one in five adults in the United states have TG of 200 mg/dL or higher, but that pharmacotherapy is utilized in less than four percent of this population (Ford 2009, Beltran-Sanchez 2013). In addition, while some success has been achieved in reducing cholesterol intake, increased total caloric intake, increased carbohydrate intake, and decreased physical activity have likely been factors in observed increases in metabolic syndrome, driven by increases in the prevalence of hypertriglyceridemia (HTG), waist circumference, and high blood pressure (Ford 2009). These metabolic syndrome-related changes are likely to be part of the reason why TG reductions have not mirrored LDL-C reductions.

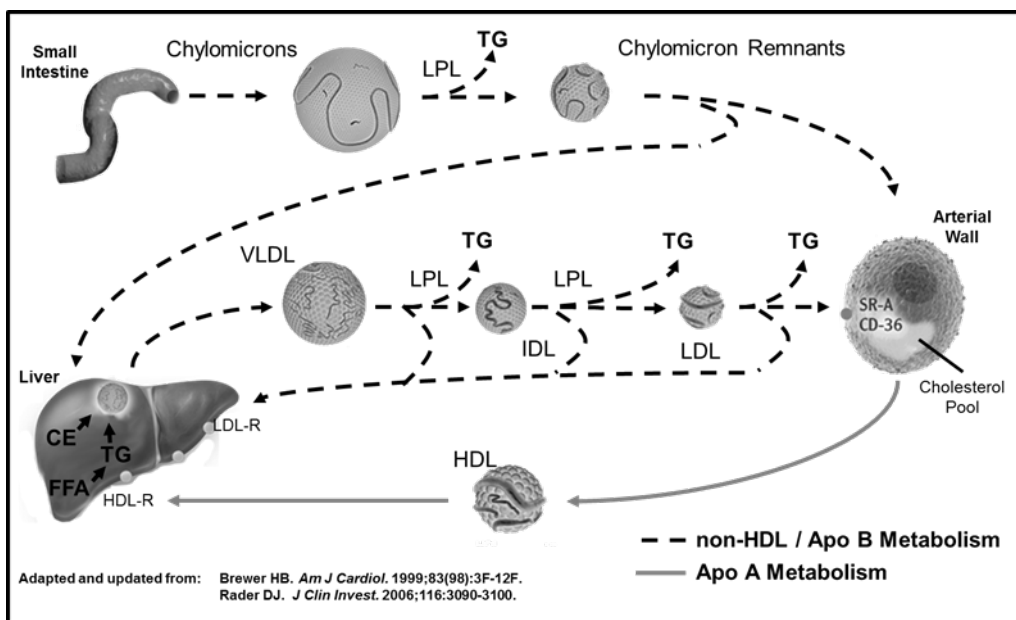
Multiple trials have demonstrated a substantial reduction in CV risk with LDL-C lowering, but not complete risk elimination. One important contributor to this residual risk is elevated non-HDL-C, driven by elevated hepatic TG and typically also presenting with low HDL-C. There has been an enduring association between elevated TG and CV risk (Austin 1998, Assmann 1996, Sarwar 2007, Otvos 2002), but it has been debated whether TG are an independent risk factor for CV disease (CVD). Such deliberation arises due to the extensive interdependence of plasma lipids and the lipoproteins that carry them.

2.3 Hypertriglyceridemia and Lipoprotein Metabolism

Lipoproteins are responsible for circulatory transport of fat and cholesterol. Chylomicrons carry lipids from the intestine to tissues throughout the body, releasing free fatty acids from TG and concomitantly decreasing in size to become chylomicron remnants, which are then taken up by the liver (Figure 5). Triglyceride levels in the

liver drive the packaging of lipids (primarily TG and cholesterol) into VLDL and subsequent release into the plasma. Like chylomicrons, VLDL particles deliver TG to peripheral tissues. As TGs are removed from VLDL, VLDL decreases in size, becoming VLDL remnants, then intermediate density lipoprotein (IDL) and then LDL. The resulting LDL (and its cholesterol) can be taken up by peripheral tissues or the liver. The cholesterol carried by chylomicron and VLDL remnants are together termed remnant lipoprotein cholesterol (RLP-C), which is elevated post-prandially and in hypertriglyceridemia. Chylomicron remnants, VLDL, IDL, and LDL are considered atherogenic particles since they can deliver cholesterol to peripheral tissues, including the arterial wall. Each of these atherogenic particles carries one apolipoprotein B (apoB) molecule. Conversely, HDL particles carry apolipoprotein A (apoA) and work to remove cholesterol from peripheral tissues and return it the liver, known as reverse cholesterol transport. HDL is therefore considered anti-atherogenic. Non-HDL-C is calculated by subtracting the cholesterol carried by HDL particles from total cholesterol. Both non-HDL-C and apoB reflect the total atherogenic lipid burden, have been associated with CVD, and are often considered better markers of CV risk than LDL-C alone, particularly in statin-treated patients.

Figure 5: Basic Overview of Lipid Metabolism

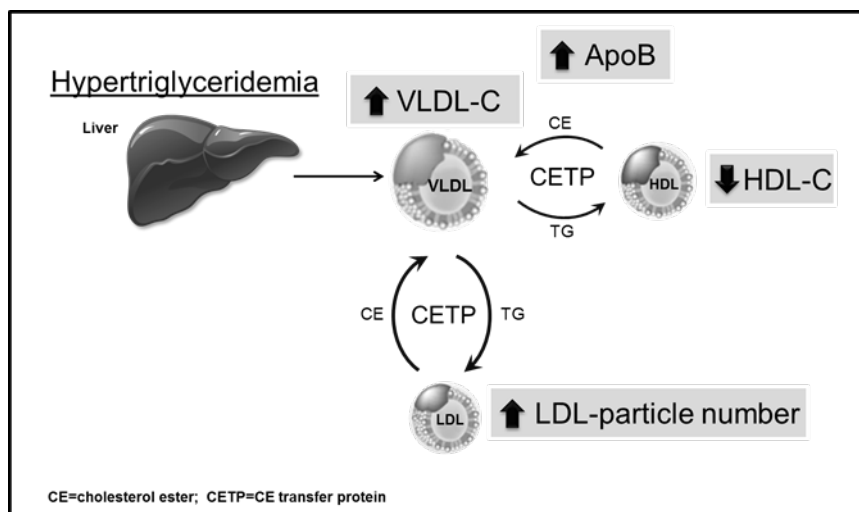


When TG levels are normal, they are quickly removed from chylomicrons and VLDL, resulting in rapid clearance of chylomicrons and conversion of VLDL to LDL. Therefore, in a non-hypertriglyceridemic patient, LDL-C carries the majority of atherogenic cholesterol and is a good marker of CV risk. On the other hand, when

TGs are elevated, chylomicrons and VLDL particles persist in the plasma and LDL-C no longer reflects the full atherogenicity of the lipid profile. TG levels are highly correlated with VLDL-C and non-HDL-C levels, and they have a strong inverse association with HDL-C (Austin 2000). This relationship of high TG, high VLDL-C and RLP-C, and low HDL-C is partially mediated by cholesterol ester transfer protein (CETP), and this CETP-mediated process also results in a decrease in LDL-P size and often an increase in LDL-P number.

In patients without elevated TG, CETP mediates transfer of cholesterol ester (CE) from HDL particles to apoB-containing particles, including VLDL and LDL, in exchange for TG. These cholesterol-enriched VLDL and LDL particles are taken up by the liver, thus providing an indirect route for HDL-C to be delivered to the liver. In HTG, the CETP mechanism is skewed. HDL loses too much cholesterol and takes on too many TG; the TG are removed by lipases and small, dense HDL (sdHDL) result (Figure 6). Small, dense HDL are unstable and undergo renal clearance, resulting in an overall decrease in HDL-C. At the same time VLDL begins to trade TG for CE from LDL, resulting in LDL with less cholesterol and more TG. As with HDL, the TG on LDL are removed by lipases, resulting in small, dense LDL (sdLDL). Importantly, unlike sdHDL, sdLDL is not efficiently cleared from the plasma, resulting in an overall decrease in LDL-C and LDL particle size, but often an increase in LDL-P number. It is important to note, that while LDL-C has decreased, the cholesterol content of VLDL (another atherogenic, apoB-containing lipoprotein) has increased. Overall, this means that HTG has induced an atherogenic lipid profile, including increased VLDL-C, decreased HDL-C, and decreased LDL-C, but increased LDL-P number.

Figure 6: Dyslipidemia in Hypertriglyceridemia



2.4 Hypertriglyceridemia and Cardiovascular Risk

The CV risk associated with both elevated LDL-C and non-HDL-C is reflected in current guidelines of ATP III and other organizations (NCEP 2002, Grundy 2004, Brunzel 2008, Berglund 2012, Jellinger 2012, ESC/EAS Guideline 2011, International Atherosclerosis Society (IAS) Position Paper 2013, Miller 2011, Garber 2013). The wealth of data supporting LDL-C lowering led to ATP III recommendations to first focus on achieving LDL-C goal. Once LDL-C goal has been met, the fuller picture of atherogenic risk is considered and treatment focus shifts to non-HDL-C goals in patients with persistently elevated TG (≥ 200 mg/dL). The evidence supporting non-HDL-C lowering in patients with elevated TG who reach LDL-C goal is derived from multiple studies showing that patients that achieve LDL-C targets continue to have elevated CV risk. The Framingham Heart Study demonstrated an increase in CHD risk with increasing non-HDL-C levels, even within the lowest LDL-C range (Liu 2006). Residual CV risk after LDL-C lowering by statins has been consistently observed across primary (Scandinavian Simvastatin Survival Study Group 1994, Sacks 1996, Heart Protection Study Collaborative Group 2002, Downs 1998) and secondary (LIPID Group 1998, Shepherd 1995) prevention trials. A recent meta-analysis of 38,153 patients treated with statins in randomized controlled trials provides further compelling evidence (Boekholdt 2012). In this meta-analysis, statin-treated patients who reached LDL-C targets (< 100 mg/dL), but had persistently elevated non-HDL-C (≥ 130 mg/dL) had a hazard ratio for incidence of CV events of 1.32 (95% CI; 1.17-1.50) relative to patients who reached both LDL-C and non-HDL-C targets. In other words, persistently elevated non-HDL-C, even when LDL-C goal was achieved, resulted in a 32% increase in residual CV risk. Non-HDL-C can be reduced by either increasing statin therapy or initiating TG-lowering therapy. Increasing the dose of a statin is not always an option in some patients, and TG-lowering therapies should be considered.

Hepatic TG are primary key driver of VLDL synthesis and release from the liver (Fisher 1997). As such, high hepatic TG lead to increased VLDL secretion and a concomitant increase in VLDL-C, non-HDL-C, and apoB. At the same time, high plasma TG are associated with a decrease in HDL-C. These interdependent, pathophysiological relationships of TG, cholesterol, and the lipoproteins that carry them explain the long-standing association between hypertriglyceridemia and CVD. While it has been established that high TG is associated with CVD, what has been under debate is whether TG represents an independent risk factor for CVD, especially once risk models are corrected for TG interdependent lipid markers such as non-HDL-C, apoB, and HDL-C. Many case-controlled (e.g. Faergeman 2009, Miller 2008), observational (e.g. Kasai 2013), and prospective (e.g. Assmann 1996) studies have demonstrated TG as a CV risk factor. Four meta-analyses demonstrated TG to be a CV risk factor, each evaluating between 17 and 68 prospective studies, representing between 57,277 and 302,430 patients per analysis (Austin 1998, Patel 2004, Sarwar

2007, ERFC 2009). However, the tight interplay between TG and other lipid parameters has resulted in the predictive value of TG to be attenuated (Assmann 1996, Faergeman, 2009, Miller 2008, Austin 1998, Patel 2004), or even lost (Sarwar 2010, ERFC 2009), when risk models are corrected for other lipid parameters such as non-HDL-C and HDL-C, ApoB, or their ratios (e.g. TC to HDL-C or apoB to apoA). This discussion highlights the variability of results regarding TG and CVD that has resulted in a decades-long debate over whether TG is an independent predictor of CV risk (Brown 1965, Hulley 1980, NIH Consensus Conference 1993). The debate discussed above regarding TG as an independent risk factor for CVD arises because of the intricate interplay between TG and non-HDL-C, HDL-C, and apoB. Due to this complex biological interdependence between TG, cholesterol, and the lipoproteins that carry them, it is challenging to design appropriate adjustments to risk models that accurately reflect physiological connections between lipids. For example, part of the atherogenic lipid profile associated with HTG is low HDL-C, so some loss of TG independence as a risk marker would be expected when models are adjusted for HDL-C. Also, the interdependence of lipids and lipoproteins is reflected in the calculations used to determine VLDL-C, which is TG/5 (for TG < 400 mg/dL). Therefore non-HDL-C includes the influence of TG and therefore any model that is adjusted for non-HDL-C has effectively already adjusted for TG. In other words, the loss of TG as an independent risk factor would be expected when a model adjusts for non-HDL-C.

Despite the debate regarding TG as an independent risk factor, TG continues to be regarded as an important biomarker of CVD based on its association with an atherogenic lipid profile. In addition, non-HDL-C has been demonstrated to be an independent risk factor for CVD, and TG levels are an important factor in the elevation non-HDL-C levels. The ATP III guideline (NCEP2002), the scientific statement from the American Heart Association on TG and CVD (Miller 2011), the consensus report from the American Diabetes Association (ADA) and the American College of Cardiology (ACC) on lipoprotein management (Brunzell 2008), and the dyslipidemia guidelines from the American Association of Clinical Endocrinology (Jellinger 2012) and The Endocrine Society (Berglund 2012) all recognize the association of increased TG levels with CV risk, and therefore support the lowering of non-HDL-C through TG reduction.

Various experimental models have been used to explore the clinically observed connection between the hypertriglyceridemic state and atherosclerosis. (Colhoun 2002) As discussed above, high hepatic TG is a driver of atherogenic dyslipidemia, including increased non-HDL-C (inclusive of VLDL-C and RLP-C) and apoB, and decreased HDL-C and LDL-P size, and likely an increase in LDL-P number. (Grundy 1995) Specifically, high TG is characterized by 1) RLPs that do not need to undergo modification (i.e, oxidation) to enter the arterial wall and 2) a high proportion of sdLDL that are more susceptible to oxidation. Oxidized LDL (ox-LDL) may increase

CV risk through unregulated uptake by arterial wall macrophages, leading to foam cell and ultimately plaque formation (Ip 2009, Chait 1993). Uptake of apoB lipoproteins in general, including RLPs, leads to foam cell formation and initiation of inflammatory cascades and chylomicron remnants have been shown to increase lipid accumulation to a level comparable with ox-LDL (Liu 2009, Batt 2004). Some of these inflammatory responses include cytokines, fibrinogen and coagulation factors (Jones 2012, Norata 2007, Shin 2004, Ting 2007, Wang 2009). Triglyceride-rich lipoproteins can also induce atherogenic changes in adhesion molecules (Kawakami 2006, Kawakami 2006), induce apoptosis (Wehinger 2007), and alter vascular function (Caron 2008). Other studies also support TG influence on proinflammatory circulating markers such as high sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A2 (LpPLA2) (Austin 1998, Assmann 1996, Tirosh 2007, Miller 2008, Barter 2006, Fruchart 2008, Sniderman 2003, NCEP 2002, Nissen 2005), and routine measurement of hsCRP is now recommended by the NLA Expert Guidance in males >50 years of age and females >60 years of age with intermediate risk for CVD [5-20% 10-year CHD risk event] (Davidson 2011). Finally, in addition to their own atherogenic effects, triglyceride rich lipoproteins (TRLs) may decrease the anti-atherogenic (lipid and inflammatory) effects of HDL particles (Palmer 2004, Patel 2009).

Taken together, TG is regarded as an important biomarker of CVD based on its association with an atherogenic lipid profile. High TG levels drive an increase in non-HDL-C, and non-HDL-C has been demonstrated to be an independent risk factor for CVD. TG-lowering therapies are important treatments used to reduce non-HDL-C.

2.5 EPA in the Treatment of Hypertriglyceridemia

Vascepa (EPA alone) and Lovaza (an omega fatty acid complex mixture consisting predominantly of EPA and DHA) are each approved TG-lowering therapies in severe hypertriglyceridemia. EPA and DHA have some similar and some divergent effects on lipid metabolism. Both EPA and DHA reduce plasma TG levels through various mechanisms, which have been thoroughly reviewed (Shearer 2012, Jacobson 2012, Russell 2012, Wei 2011) and will be briefly discussed here. EPA and DHA reduce TG synthesis, reduce VLDL production and secretion, and likely increase plasma TG clearance. Measurements of increased TG clearance with EPA+DHA treatment have been inconsistent, likely due to the complex relationship between VLDL secretion and the fractional catabolic rates of VLDL and TG. Nonetheless, randomized, controlled studies have demonstrated an increase in both chylomicron-TG clearance and VLDL conversion to IDL (as a result of TG removal) (Shearer 2012). On the other hand, reduction of hepatic VLDL-TG production and VLDL secretion has been well demonstrated in kinetic tracer studies in humans. VLDL assembly is complex and regulated by TG availability, which is tightly coordinated with apoB and microsomal

TG transfer protein (MTP). MTP facilitates TG incorporation onto nascent apoB in the liver. EPA and DHA decrease hepatic apoB and MTP mRNA (Lopez-Soldado 2009), and stimulate degradation of the apoB protein. Part of this effect may be due to the decrease in hepatic non-esterified fatty acids (NEFA) available for incorporation into TG (EPA and DHA increase hepatic β -oxidation) and inhibition of TG synthesis (EPA inhibits diacylglycerol acyltransferase (DGAT) activity).

In further consideration of hepatic NEFA levels available for TG synthesis, NEFA can arrive at the liver through diet (chylomicron delivery), de novo synthesis, or circulating NEFA. Circulating NEFA may account for between 78-95% of hepatic NEFA levels, and plasma NEFA can be particularly elevated in the diabetic state. EPA and DHA may reduce circulating NEFA (observed in healthy subjects taking approximately 9 g/day; Dagnelie 1994). Mechanistically, EPA and DHA may decrease plasma NEFA by stimulating the uptake and oxidation of free fatty acids in cardiac, skeletal, and adipose tissues, and by decreasing their release from adipocytes. This would result in a decrease in the plasma NEFA pool; thereby ultimately decreasing the level of NEFA available for hepatic TG synthesis.

While having many similarities, EPA and DHA do not have identical effects on plasma lipids, as demonstrated in 22 randomized, controlled trials reviewed by Jacobson et. al. (Jacobson 2012). For example, across the six head-to-head studies of EPA versus DHA (of varying doses, study formulations, sample sizes, and study designs), EPA treatment appears to modestly decrease LDL-C (average decrease of $0.7 \pm 4.2\%$) or have a neutral effect, while DHA therapy tends to increase it (average change of $2.6 \pm 4.3\%$). Across these same studies, with baseline TG values ranging from >150 to <664 mg/dL, decreases in TG were observed with both therapies ($-15.6 \pm 12.3\%$ with EPA; $-22.4 \pm 13.3\%$ with DHA). Non-HDL-C was decreased by both therapies, with slightly greater effects from EPA versus DHA therapy (net effect of an additional 1.7% decrease). HDL-C increased, on average, to a greater extent with DHA versus EPA treatment (net effect of an additional 5.9% increase). While general trends can be observed, it is important to note that across the 22 studies there was a range of EPA or DHA doses used (0.75-4 g/day), a broad spectrum of patients studied, and baseline lipids were highly variable (e.g., TG levels ranged from <150 to >650 mg/dL and LDL-C levels ranged from 76.8 to 213 mg/dL). Therefore percent changes discussed here cannot be directly applied to any specific patient population.

Some possible explanations for the differential effects of EPA and DHA have been provided by in vivo, in vitro, and some clinical studies (Mozaffarian 2012). For example, diacylglycerol acyl transferase (DGAT) controls a key step in TG synthesis in the liver and EPA, but not DHA, appears to be a poor substrate for diacylglycerol acyl transferase (DGAT) and inhibits its activity (Madsen 1999, Berge 1999). Peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription

factors that regulate the expression of enzymes and proteins involved in lipid regulation. PPAR α increases both LPL levels and NEFA β -oxidation in the liver, adipose, and skeletal and cardiac muscle. In rat hepatocytes, EPA has been found to be a potent simulator of PPAR α , while DHA only a weak activator (Jump 2008), which may account for some of the increased LPL activity observed with EPA (Vaagenes 1999). From conformational studies, it appears that EPA may also be a stronger activator of PPAR α (Forman 1997). On the other hand, sterol regulatory element binding proteins (SREBP) are transcription factors that also regulate genes involved in lipid regulation, including the LDL receptor (LDL-R). SREBPs are the primary hepatic activators of lipogenesis and both EPA and DHA inhibit SREBP gene expression, but availability of the functional, nuclear forms of SREBPs (nSREBP) appear to be reduced only by DHA (Jump 2008, Botolin 2006). This may be partially due to preferential hepatic uptake of DHA-loaded VLDL. More specifically, cells treated with DHA-loaded VLDL were a more potent competitor of hepatic LDL-R (versus control or EPA-loaded VLDL) and resulted in reduced LDL-R mRNA and expression, and concomitant reductions in LDL-R-mediated uptake. EPA-loaded VLDL did not have these same effects (Ishida 2013). Taken together, the above studies suggest that EPA is a more potent activator of plasma TG clearance (LPL activity) and NEFA utilization (β -oxidation). At the same time, DHA may be a more potent down-regulator of the lipid synthesis, as well as the LDL-R, resulting in decreased clearance of apoB-containing lipoproteins. These differential effects of EPA and DHA on lipid metabolism may explain the differences in lipoproteins and their lipid content observed in clinical studies.

Overall, EPA and DHA are effective at reducing TG and non-HDL-C. Some of the postulated mechanisms whereby EPA and DHA alter lipids overlap, and some appear to be distinct.

2.6 EPA and Cardiovascular Disease

Omega-3 fatty acids, the most studied of which are EPA and DHA, have been speculated to have cardiovascular benefit for decades, even beyond their TG-lowering effects. And yet, the evidence linking omega-3 fatty acid treatment with reduced CV risk is mixed. Further, EPA may have some CV benefits that are distinct from those of DHA. The scientific literature also indicates that other omega fatty acids derived from fish oil have biological effects. For instance, the manufacturer of Lovaza noted that “experimental evidence suggests that the individual omega-3 fatty acids EPA, DHA, docosapentaenoic acid (DPA), stearidonic acid (SDA), heneicosapentaenoic acid (HPA), and alpha-linolenic acid (ALA) are each either biologically active or are metabolized in the body to form biologically active agents” (Citizen Petition 2009). How different omega acid components work together to produce clinical effects observed in patients is not completely understood. No studies have been conducted to

elucidate the relative contribution of individual omega acid constituents within a particular complex mixture or any combination of various mixed constituents. It should be noted that many studies featured in the scientific literature as studies of EPA and DHA in combination are, in fact, studies of more complex mixtures of omega fatty acids containing EPA and DHA as the predominant by weight constituents (i.e., either Lovaza itself, its European counterpart, Omacor, or a dietary supplement). For simplicity, we generally use the term omega acid mixtures to describe such compositions. Where it is not known that a studied composition consists of an omega acid mixture containing more than EPA and DHA, we refer to such compositions consistent with the respective study paper author's description, typically as a study of EPA+DHA.

We will begin with a general discussion of omega acid mixtures and then move into some of the EPA-specific data. Some meta-analyses have shown a beneficial effect of treatment with omega acid mixtures on CV outcomes (Delgado-Lista 2012, Casula 2013, Marik 2009), while others noted that the benefits may not be as great as previously believed (Kotwal 2012, Filion 2010), and others have shown a lack of benefit (Rizos, Kwak 2012). Most of these meta-analyses did not sufficiently include/exclude studies with important potential confounding factors, which varied widely across the studies. These include non-TG lowering (and, on a background of statin therapy, potentially non-therapeutic) doses of omega acid mixtures (most ≤ 1 -2 g/day; resulting from dietary advice to increase fish intake up to 10 g/day), wide variation of concomitant lipid-lowering medications, mixed patient populations (e.g., healthy versus CVD patients), large variations in study designs (e.g., open-label versus placebo-controlled), small study sizes (e.g., as small as 50 patients), follow-up periods that were too short (including less than one year), and choice of placebo (e.g., none, or lipid altering oils such as olive oil). To this point, meta-analyses that only included randomized, controlled studies of at least one year in patients with a history of CV disease found statistically significant reductions in CV outcomes. Casula et al. only included studies of at least 1 g/day omega acid mixtures and found significant reductions in cardiac death (RR 0.68, 95% CI 0.56 to 0.83), sudden death (RR 0.67, 95% CI 0.52 to 0.87), and myocardial infarction (RR 0.75, 95% CI 0.63 to 0.88) (Casula 2013). Marik et. al. included EPA+DHA doses of 0.27 to 4.8 g/day (only one study below 1 g/day; average 1.8 ± 1.2 g/day) and found significant reductions in CV deaths (OR 0.87, 95% CI 0.79 to 0.95), sudden cardiac death (OR 0.87, 95% CI 0.76 to 0.99), all-cause mortality (OR 0.92, 95% CI 0.85 to 0.99), and nonfatal CV events (OR 0.92, 95% CI 0.85 to 0.99) (Marik 2009). While not conclusive, it would appear that omega acid mixtures provides a beneficial drop in CV risk in well designed, placebo-controlled trials of at least a year in duration, especially in patients with CVD. Included in some of these meta-analyses, are several outcomes trials addressing omega acid mixtures of predominantly EPA+DHA, or EPA alone, in CVD. These trials

provide some insights into appropriate EPA dosing, patient populations, and benefits of EPA therapy.

Most primary and secondary outcomes trials addressing omega acid mixture treatment and CVD focused on mixtures predominantly comprised of EPA+DHA, while one focused on EPA alone (Marchioli 2002, GISSI-HF Investigators 2008, Kromhout 2010, Rauch 2010, Galan 2010, ORIGIN Trial Investigators 2012, The Risk and Prevention Study Collaborative Group 2013, Yokoyama 2007). The eight outcomes trials are summarized in Table 3. We will start by looking at the seven studies using omega acid mixtures, and within these studies, will focus on the omega acid mixture treatment arms. First, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico – Prevenzione (GISSI-P) (Marchioli 2002) randomized over 11,000 patients with recent (≤ 3 month) myocardial infarction (MI) to receive either an omega acid mixture (containing 850 mg/day of EPA+DHA), vitamin E, both, or none for 3.5 years. Omega acid mixture treatment resulted in a significant 14% lower risk in the primary combined endpoint of death, non-fatal MI, and stroke. Of note, a slight, but significant, reduction in TG was observed (-4.6% with omega acid mixture versus $+0.4\%$ in control). The most readily apparent drawbacks to this study were the relatively low dose of EPA+DHA (850 mg/day), that it was not placebo controlled, and that cholesterol-lowering agents were added on an as needed, per-patient basis, with less than half (45.5%) of the patients on a cholesterol-lowering agents by the end of the trial.

Table 3 Omega Acid Mixture or EPA-only Outcomes Trials

Study	Population	Baseline LDL-C [mg/dL]	Baseline TG [mg/dL]	Interventions	Duration (years)	Primary Endpoint	Outcomes (CI)
Omega acid mixture studies							
GISSI-P	11,324 pts recent MI (≤3 mon)	137	163	850 mg EPA+DHA vs. Vit E vs.n-3+Vit E vs. placebo	3.5	Death+non-fatal MI/stroke	RR = 0.85 (0.74 to 0.98) [four way analysis]
GISSI-HF	6975 pts symptomatic HF	Not provided	126	850 mg EPA+DHA vs. placebo	3.9	Co-primary of death, and death or CV hospitalization	Death HR: 0.91 (0.833– 0.998) Death or CV hospitalization HR: 0.92 (0.849–0.999)
OMEGA	3851 pts recent MI (≤2 wks)	Not provided	Not provided	840 mg EPA+DHA vs. placebo	1	SCD	OR = 0.95 (0.56 to 1.60)
Alpha-Omega	4837 pts history of MI (median 3.7 yrs)	99-102	144-150	376 mg EPA+DHA vs. placebo and ALA (1.9 g combined)	3.4	MACE	HR = 1.01 (0.87–1.17)
SU.FOL.OM3	2501 pts recent coronary or cervical ischemic event (median 101 d)	104	106	600 mg EPA+DHA vs. placebo and B vitamin	4.2	MACE	HR = 1.08 (0.79 to 1.47)
ORIGIN	12,536 pts dysglycemia	112	140-142	840 mg EPA+DHA vs. placebo	6.2	CV death	HR = 0.98 (0.87–1.10)
Risk & Prevention	12,505 pts high risk CVD	132	150	840 mg EPA+DHA vs. placebo	5	CV death or CV hospital admission	HR = 0.98 (0.88–1.08)
Pure EPA Study							
JELIS	18,645 pts hyper-cholesterolemic	182	152-163	1800 mg EPA + statin vs. statin	4.6	Any major coronary event	HR = 0.81 (0.69–0.95)

Second, the GISSI-Heart Failure (GISSI-HF) (GISSI-HF Investigators 2008) study was a randomized, double-blind, placebo controlled trial of approximately 7,000 chronic heart failure patients who received either an omega acid mixture (containing 850 mg/day of EPA+DHA) or placebo, and were followed for an average of 3.9 years. GISSI-HF demonstrated small, statistically significant benefits of omega acid mixture treatment in the primary endpoints of death (HR 0.91) and death/hospitalization for CV reason (HR 0.92). Slight decreases in TG were observed in patients taking the omega acid mixture, dropping from 126 mg/dL at baseline, to 120 mg/dL at one year, and to 119 mg/dL at 3 years (interaction time versus treatment $p < 0.0001$). As with GISSI-P, the low dose of EPA+DHA (850 mg/day) is a drawback to this study, as was the fact that only about 22-23% of patients were on statin therapy.

Third, the Alpha Omega Trial (Kromhout 2010) was a double-blind, placebo-controlled trial that randomized almost 5,000 post-MI patients to a daily targeted use of one of four margarines: 400 mg/d EPA+DHA, 2000 mg alpha linolenic acid (ALA), EPA+DHA+ALA, or placebo for 40 months. EPA+DHA margarine did not significantly reduce the primary endpoint of major CV events. The Kaplan-Meier curve for fatal coronary heart disease showed a lower risk in the EPA+DHA treated group up until about 30 months, but this effect was lost by the end of the trial. A post hoc analysis of diabetic patients did show a significant reduction in fatal heart disease (HR 0.51) and arrhythmia-related events (HR 0.51) with EPA+DHA therapy. No statistically significant changes in TG were observed with EPA+DHA treatment relative to placebo. The most noticeable drawbacks to this study were the low dose of EPA+DHA (intake averaged 376 mg/day), the relatively high background median intake of EPA+DHA (130 mg/day vs. standard intake in the United States of 20 mg/day), the inconsistency of delivery dose through margarine use, the potential dietary changes required for administration (about 4 slices of bread per day), and that 15% of patients were not on statin therapy. In addition, the study was only powered at 35% to observe a hazard ratio of 0.75 for fatal heart disease (Kromhout 2010).

Fourth, the OMEGA Trial was a randomized, double-blind, placebo-controlled study in approximately 3,800 recent post-MI patients treated with an omega acid mixture (containing 840 mg/day EPA+DHA) for one year (Rauch 2010). No significant effects were observed on the primary outcome of sudden cardiac death. There was a modest, but statistically significant benefit of lower end of study TG with omega acid mixture treatment (121 mg/dL for omega acid mixture versus 127 mg/dL for placebo, $p < 0.01$). Patients were on current standard of care therapy, including statin use in approximately 94% of the study population. The most glaring drawback of this study was that it was clearly underpowered, as discussed by the authors, with a power of 44% to detect a 45% risk reduction in sudden cardiac death. Other drawbacks include the low dose of EPA+DHA (840 mg/day), relatively short treatment period (one year), and high

background fish intake (45% of patients ate fish several times a week).

Fifth, the Supplementation with B Vitamins and Omega-3 Fatty Acids Trial (Galan 2010) was a double-blind, placebo-controlled trial that randomized approximately 2,500 patients with a history of MI (median time from onset =101 days), unstable angina, or ischaemic stroke to receive an omega acid mixture (containing 600 mg/day EPA+DHA) for a median of 4.7 years. No significant effects were observed on the primary endpoint of major coronary events (non-fatal MI, stroke, death from CVD). Changes in TG levels were not reported. The use of statin therapy was not specifically shown, but approximately 85% of the study population was using lipid lowering agents. Once again, the strongest drawbacks of this study were that it was underpowered (with a power of 44% to detect at 25% risk reduction in the primary endpoint), and utilized a low dose of EPA+DHA (600 mg/day).

Sixth, the ORIGIN Trial (ORIGIN Trial Investigators 2012) was a double-blind, placebo-controlled trial that randomized over 12,000 patients with dysglycemia in a two-by-two factorial design to receive an omega acid mixture (containing 840 mg/day EPA+DHA) for an average of 6.2 years. No significant effects were observed on the primary outcome of CV death. There was a modest, but statistically significant, decrease in TG (-23.5 mg/dL for omega acid mixture versus -9.0 mg/dL for placebo, $p<0.001$). Bleeding was reported in 57 patients receiving omega acid mixture versus 65 receiving placebo, with intracranial bleeding reported in 42 patients receiving omega acid mixture versus 51 receiving placebo. The authors note that there were no significant between-group differences in plasma glucose or glycated haemoglobin. The main drawbacks of this study were the low dose of EPA+DHA (840 mg/day), the relatively high EPA+DHA background intake (mean intake of 210 mg/day vs. standard intake in the United States of 20 mg/day), and the fact that only about 54% of the patients were on statin therapy.

Seventh, the Risk and Prevention Study (The Risk and Prevention Study Collaborative Group 2013) was a double-blind, placebo-controlled trial that randomized over 12,000 patients to receive an omega acid mixture (containing 840 mg/day EPA+DHA) for a median of five years. No differences were observed in the primary endpoint of death from cardiovascular causes or admission to the hospital for cardiovascular causes. There was a modest, but statistically significant, decrease in TG (-28.2 mg/dL for omega acid mixture versus -20.1 mg/dL for placebo, $p<0.001$). The occurrence of bleeding was similar between treatment groups (0.3% of omega acid mixture treated patients versus 0.2 % of placebo treated, $p=0.44$). There were also no differences in fasting plasma glucose (-3.963 ± 0.570 for omega acid mixture versus -5.441 ± 0.573 for placebo, $p=0.07$) or glycated haemoglobin (HbA1c, -0.024 ± 0.031 for omega acid mixture versus -0.047 ± 0.031 for placebo, $p=0.59$) with omega acid mixture treatment versus placebo. The main drawbacks of this study were the low dose of EPA+DHA

(containing 840 mg/day) and the lower than expected event rate, suggesting the study might have been underpowered.

To summarize the seven CV outcomes trials testing omega acid mixtures, at least nominally of EPA+DHA therapy, two demonstrated significant primary endpoint risk reduction, one demonstrated CV risk reduction only in the post hoc analysis of diabetic patients, and four did not demonstrate benefit. All seven of these trials had design limitations, but key consistent limitations were low omega acid dosing (containing 376-850 mg/day EPA+DHA), possible underutilization of statin therapy, and lack of statistical powering. It is also worth noting that of the six studies that reported LDL-C, median levels were relatively low (95-137 mg/dL). Median TG were also relatively low across the studies (106-185 mg/dL), with all seven studies being below 200 mg/dL. These patients therefore do not necessarily represent patients presenting with persistent HTG, despite LDL-C being treated to goal.

One CV outcomes trial has looked specifically at the effects of EPA – without DHA and other omega acids – therapy on CV risk reduction. The Japan EPA Lipid Intervention Study (JELIS) (Yokoyama 2007) randomized over 18,000 primary and secondary prevention patients with elevated total cholesterol (>250 mg/dL) to a statin alone or a statin plus EPA (1.8 g/day). Patients were followed for an average of 4.6 years for a composite primary endpoint of any major coronary event, including sudden cardiac death, fatal and nonfatal MI, and non-fatal events; including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. Compared to statin therapy alone (control), statin plus EPA treatment resulted in a significant 19% relative risk reduction in the primary endpoint (HR 0.81, 95% CI 0.69 to 0.95). Baseline TG levels were low (152-163 mg/dL), and yet EPA plus statin therapy resulted in a modest, but statistically significant reduction in TG (9% reduction compared to 4% reduction with statin-only treatment, $p < 0.0001$). Baseline LDL-C was somewhat high (182 mg/dL), and was reduced 25% in both treatment groups (no difference between statin-only and EPA + statin treatment). Safety findings included a slight increase in adverse events coded as gastrointestinal disorder (3.8% on EPA and 1.7% on control; $p < 0.0001$), hemorrhage (1.1% on EPA compared to 0.6% on control, $p = 0.0006$) and abnormal laboratory tests (4.1% on EPA compared to 3.5% on control; $p = 0.03$); which included a non-significant increase in blood sugar (0.4% on EPA compared to 0.3% on control; $p = 0.17$). Concerning bleeding, the authors noted no between-group differences in stroke, including cerebral and/or subarachnoidal bleeding. Additionally, there were no between group differences reported for the rate of cancer. The main drawback to this study was that it was not placebo controlled. However, the study employed an EPA dose (1.8 g/day) that was 2.1- to 4.8-fold higher than the EPA+DHA doses used in the seven omega acid mixture trials discussed previously (376-850 mg/day). In addition, all patients in the JELIS study were on statin therapy (\pm EPA), although the statin doses (pravastatin 10 mg/day and simvastatin 5 mg/day) used are

not reflective of doses used in non-Japanese population. Nonetheless, statin use across the study may be a more accurate reflection of current treatment guidelines for patients with, or at risk for, CV disease.

There are some additional important points when considering the appropriate application of the JELIS results. First, JELIS is the only outcomes study ever conducted to demonstrate a CV benefit of adding a lipid-altering drug to statin therapy. Regarding the therapeutic dose of EPA, the JELIS study was performed in an exclusively Japanese population, which is known to have a considerably – about five times – higher fish intake than Western populations. This high fish consumption was reflected in the fact that the JELIS study population had an average baseline plasma EPA level almost ten-fold higher than the average level recorded in the United States (2.9 mol% in JELIS relative to the 0.3 mol% in the United States). Therefore, if a threshold EPA level is needed for therapeutic effects; higher doses of EPA may need to be considered in populations where fish consumption is lower than observed in Japan.

Second, a comparison of EPA blood levels in relevant trials suggest that 4 g doses of EPA provide similar EPA blood levels in the Western population studied when compared to the post-1.8g EPA-dose Japanese population studied in JELIS. As reported by Itakura, mean plasma EPA in the Epadel group (n=8321) increased from 97 µg/mL (baseline) to 170 µg/mL. (Itakura 2010). Similar effects were observed in patients treated with 4 g/day Vascepa in the MARINE study, in which mean plasma EPA increased from 61 µg/mL to 327 µg/mL (n=69), and in the ANCHOR study, in which mean plasma EPA increased from 28 µg/mL to 183 µg/mL (n=71).

Third, baseline LDL-C levels in JELIS were relatively high (182 mg/dL, reducing 25% with statin ± EPA), TG levels were relatively low (152-163 mg/dL, reducing 4 or 9% with statin or statin+EPA treatment, respectively), and statin ± EPA therapies were initiated concomitantly, which does not accurately reflect the patient population and treatment sequence that would be used in the United States to treat hypertriglyceridemic (200 to ≤ 500 mg/dL) patients with elevated LDL-C. Nonetheless, the similar reductions of LDL-C with statin ± EPA, and the additional decrease of TG with statin+EPA over statin alone, support other studies demonstrating a reduction in TG when EPA treatment is added to statin therapy, without perturbation of LDL-C.

Finally, the JELIS investigators also performed subanalyses of patients with abnormal lipid levels, defined as TG > 150 mg/dL and HDL-C <40 mg/dL. Compared to patients with normal serum TG and HDL-C levels, those with abnormal levels had significantly higher coronary artery disease hazard ratio, and EPA treatment suppressed the risk of coronary artery disease by 53% in this higher risk population (HR: 0.47; 95% CI: 0.23–0.98; p=0.043) (Saito 2008).

It is important to note that despite some outcomes studies suggesting CV benefit from therapies containing EPA or EPA+DHA, no outcomes study thus far has addressed the potential CVD benefit of lowering TG in HTG patients. Instead, CVD outcomes studies either did not have patients with substantially increased baseline TG levels (106-163 mg/dL), or they relied upon post-hoc analysis of HTG population subsets.

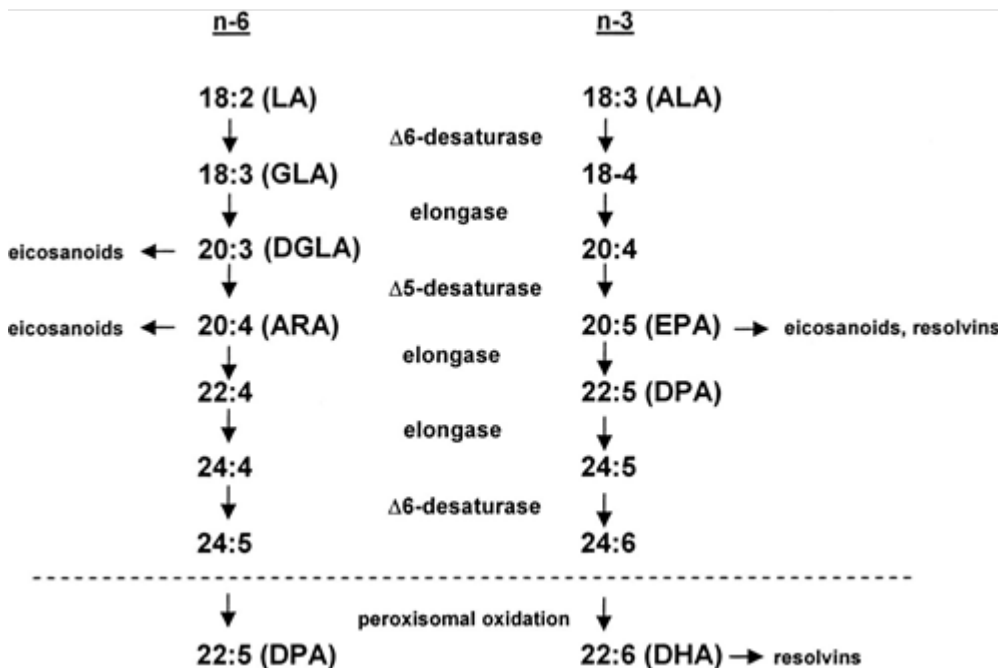
In addition to lowering TG, omega acid therapy may lead to reduced CV risk through other potential non-cholesterol mechanisms, but the exact mechanisms by which omega acids may exert such benefit are not completely understood. Some of the possible mechanisms have been reviewed by Mozaffarian et.al. (Mozaffarian 2011, Mozaffarian 2012). These mechanisms include changes in lipid profiles (Harris 2008), lipid uptake into the arterial wall (Chang 2010), plaque stabilization (Thies 2003), endothelial function (Geleijnse 2002, Mozaffarian 2005, Wang 2012, Yamakawa 2012), vascular function (Sasaki 2012), arterial stiffness (Pase 2011), vasodilation (Tagawa 1999), carotid intima-media thickness (Mita 2007), heart rate and blood pressure (Morris 1993, Mori 2010), heart failure (Djousse 2012, Gissi-HF 2008, Yamagishi 2008), oxidative stress (Mori 2003), and anti-inflammatory properties (systemic and endothelial) (Calder 2010, Aaresetoe 2012, Serhan 2008, Wall 2010, DeCaterina 1994, Caughey 1996, Jinno 2011). Of note, EPA+DHA have been proposed to benefit arrhythmic properties (Leaf 2005, Mozaffarian 2004, Gillet 2011, Anand 2008), which has been supported by at least one meta-analysis (Costanzo 2013), but not by others (Khoueiry 2013, Cao 2012, Armaganijan 2011), and may depend on the specific patient populations being studied.

The vast majority of studies addressing the effects of omega acids on CV risk have studied mixtures of omega acids comprised primarily of EPA+DHA. As stated earlier, the scientific literature also indicates that other omega fatty acids derived from fish oil have biological effects. For instance, the manufacturer of Lovaza, an FDA approved complex mixture of omega acids comprised primarily of EPA and DHA, noted that “experimental evidence suggests that the individual omega-3 fatty acids EPA, DHA, DPA, SDA, HPA, and ALA are each either biologically active or are metabolized in the body to form biologically active agents”(Citizen Petition 2009). How different omega acid components work together to produce clinical effects observed in patients is not completely understood. No studies have been conducted to elucidate the relative contribution of individual omega acid constituents within a mixture or any combination of various mixed constituents. Nonetheless, potential differential effects have been reviewed by Mozaffarian and Yu (Mozaffarian 2012) and will be briefly summarized here, with a focus on differences between EPA and DHA, as opposed to similarities. Distinctions in the effects of EPA and DHA on biologic pathways have been suggested.

As seen in the figure below, various omega-3 and omega-6 fatty acids contained in

Lovaza undergo a complex cascade of conversions and retroconversions (not illustrated) that likely alter the availability and activity of each Lovaza constituent.

Figure 7: Biochemical pathway for the interconversion of n-6 and n-3 fatty acids (Arterburn 2012, Citizen Petition 2009)



ALA, α linolenic acid; ARA, arachidonic acid; DGLA, dihomo- γ -linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid

Pronova itself notes that “[h]ow the different omega-3-acid ethyl ester components work together to produce the triglyceride lowering clinical effects observed in patients is also not well understood” (Citizen Petition 2009). For instance, DPA, a constituent of Lovaza, is also a known metabolite of EPA. DPA is dose-dependently increased in plasma and red blood cells upon Vascepa dosing (Braeckman 2013), but not Lovaza dosing (Krokan 1993). This result is counterintuitive since exogenous DPA is ingested by patients taking Lovaza, but not by those taking Vascepa. The mechanism responsible for this difference is not known although it is possible that the presence of other omega-3 fatty acids in Lovaza may inhibit the elongase enzyme responsible for DPA production. While the clinical effects of this and similar differences are unknown, it is clear that the complexity of the cascade may fundamentally alter or neutralize the pharmacology that would be demonstrated by an individual constituent if tested alone. This cascade may play a key role in the clinical differences seen between Vascepa and Lovaza and suggests that any assumptions about activity of various constituents in the mixture warrant careful testing.

These distinctions may also arise from differential incorporation of EPA and DHA into lipid membranes, especially lipid rafts (specialized lipid domains that play an important role in membrane associated/incorporated proteins and cell signaling), but

direct comparison of EPA and DHA is still limited. Some variability of cardiac tissue incorporation and responsiveness to diet has been observed; DHA is present at higher levels than EPA in human myocardial membranes, but EPA levels are more responsive to dietary changes. Some ion channels are located within rafts, and differences in ion channel effects have been observed; DHA being a stronger inhibitor of the ultra-rapid, delayed-rectifier K⁺ current, but EPA being a stronger inhibitor of the voltage-gated Na⁺ current. In consideration of other biologic pathways, comparison of EPA versus DHA effects on arachidonic acid metabolites (involved in inflammatory processes) is in the very early stages, but some studies suggest EPA may be a stronger inhibitor than DHA. In addition, EPA and DHA are both precursors to a newly established group of anti-inflammatory molecules (specialized pro-resolving mediator, SPM), but DHA is metabolized to more classes of SPM than EPA. In regard to oxidative stress, EPA appears to lead to a decrease in the formation of ox-LDL (Garrido-Sanchez L, 2008). Circulating LDL particles with extensive oxidization may be less able to bind to LDL receptors compared to un-oxidized LDL (Glass 2001). Conversely, oxidized LDL particles may undergo unregulated uptake by subendothelial macrophages, promoting accumulation and death of foam cells, endothelial toxicity, and atherogenesis. It is therefore possible that a decrease in LDL oxidation with EPA-only therapy may increase LDL-P clearance through increased LDL receptor recognition, and may also explain potential anti-atherosclerotic benefits of EPA-only therapy. In addition to the lipid changes discussed earlier, some physiologic risk factors are affected differently by EPA versus DHA. Resting heart rate and blood pressure appear to be lowered by DHA, but EPA effects are equivocal and less likely. Finally, in a comparison of various clinical studies evaluating EPA or DHA (including JELIS), Mozaffarian and Wu (Mozaffarian 2012) suggest that EPA may reduce the risk of nonfatal CV outcomes, while DHA appears to be less strongly related to such nonfatal endpoints. Overall, while EPA and DHA have many overlapping biologic and physiologic effects related to CV risk, some distinctions are emerging and further research is needed to clarify these distinctions.

2.7 EPA Metabolism

To understand how EPA may be affecting lipid metabolism and CV risk, we will briefly review EPA metabolism. EPA and DHA are both omega-3 fatty acids that are found in significant quantity in cold water fish and to a lesser extent in egg, plants and many other sources. Dietary supplements, and one FDA approved complex mixture of omega fatty acids, contain both DHA and EPA. Vascepa is a highly purified formulation of only EPA.

After oral administration, and similar to other long-chain fatty acid ethyl esters, EPA ethyl ester is de-esterified to the free fatty acid form, incorporated into mixed micelles,

and absorbed at the small intestine. Once in the small intestine, EPA is assembled into TG, which are then incorporated into chylomicrons and released into systemic circulation through the thoracic duct lymphatic system. In humans, peak plasma concentrations of EPA occur approximately five hours after oral dosing. Once in the plasma, EPA can be delivered to tissues throughout the body for various uses, including energy (β -oxidation) and incorporation into complex lipids in circulation and cellular membranes. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesterol esters; with less than one percent present in the unesterified form. Of the plasma unesterified EPA, greater than 99 percent is bound to plasma proteins.

EPA is mainly metabolized by the liver and muscle via beta-oxidation (β -oxidation), similar to metabolism of other dietary fatty acids (Ishiguro 1988b, Frøyland 1997, Du 2010). Beta-oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle or by conversion into ketones. Cytochrome P450- and cyclooxygenase/lipoxygenase (COX/LOX)-mediated pathways acting on EPA may lead to metabolites of EPA with potent activities, but they are only minor contributors to the metabolism and elimination of EPA (Konkel 2011). The plasma elimination half-life of EPA is approximately 89 hours. EPA does not undergo renal excretion.

2.8 Summary of Unmet Medical Need in Hypertriglyceridemia

Many patients who have benefited from well controlled LDL-C have persistent CV risk. Non-HDL-C has been established as an independent marker of CV risk and therefore represents at least some of the residual risk observed in patients with LDL-C at goal. Due to the tight physiologic relationships between TG, cholesterol, and the lipoproteins that carry them, a debate about TG as an independent marker of CV risk continues. Nonetheless, TG continue to be recognized as an important biomarker of an atherogenic state, and reductions in non-HDL-C are recommended when TG are ≥ 200 mg/dL. TG-lowering therapy is an important tool for lowering non-HDL-C. In fact, a meta-analysis of clinical trials that measured non-HDL-C found a 1:1 relationship between % non-HDL-C lowering and CHD risk reduction (Robinson 2009).

Triglycerides are considered an important biomarker of CV risk because high TG result in atherogenic dyslipidemia, including increased non-HDL-C, VLDL-C, RLP-C, apoB, and LDL particle number, and decreased HDL-C. The hypertriglyceridemic state is associated with induction of an atherogenic milieu within the arterial wall, leading to increases in plaque-forming processes. Increased uptake of lipids by macrophages leads to foam cell formation, increased inflammatory responses, increased apoptosis, and decreased vascular function. The hypertriglyceridemic state

is also associated with increased plasma markers of inflammation (hsCRP and LpPLA2) and inhibition of the anti-inflammatory and cholesterol-removal processes of HDL-C. The atherogenicity of the HTG state is observed in the PROVE IT-TIMI 22 study, where low on treatment TG (< 150 mg/dL) and low on treatment LDL (<70 mg/dL) was associated with reduced risk of recurrent CHD events compared with higher levels of TG, LDL-C or both. For each 10 mg/dL decrease in TG, CHD risk was reduced by 1.8% (Miller et al, 2008).

Meta-analyses and outcomes trials have been inconsistent regarding the benefit of omega acid mixtures in CV disease. Nonetheless, CV risk reduction was observed when meta-analyses included only well designed, controlled trials with at least 1 g/day of omega acid mixtures and of at least one year in duration. Results of outcomes trials have also varied, but taken together suggest CV benefit when higher (i.e., therapeutic) doses of omega acid mixtures are employed (at least 1 g/day; likely at least 2 g/day in the presence of statin therapy). Omega acid mixtures and EPA-only therapies have each demonstrated a minimal side effect profile across studies.

Currently approved TG-lowering therapies have specific limitations that reduce either their compliance (e.g., flushing with niacin) or their potential utility in combination therapy with statins (e.g., increased myopathy with niacin and fibrates; LDL-C increase with off-label use of the prescription omega acid mixture). EPA-only therapy provides a much needed option for TG-lowering that can safely and effectively added on to a statin to lower TG, VLDL-C, LDL-C, ApoB, LpPLA2 and non-HDL-C.

3. Overview of Vascepa and Clinical Development

3.1 Summary

- Vascepa is absorbed through the same pathways as other long chain fatty acids.
- No Vascepa drug-drug interactions were observed with typical substrates of four key cytochrome P450 enzymes involved in the processing of a wide array of compounds.
- Prior experience with EPA suggests that a Vascepa dose of 4 g/day would provide meaningful TG reductions.
- Prior Vascepa safety experience supports the use of 4 g/day.
- The Vascepa CV Development Program consists of three randomized, placebo-controlled, Phase 3 studies in hypertriglyceridemia; two completed and one ongoing.
- An FDA SPA agreement was reached for the ANCHOR study, which included the primary endpoint of TG reduction, a prespecified analysis of non-inferiority for change in LDL-C, and that review of an application for Vascepa treatment of HTG (200 to ≤ 500 mg/dL), in patients with LDL-C at goal through statin therapy, would occur after patient enrollment in REDUCE-IT reached 50%. Each of these endpoints were achieved.

3.2 Overview of Vascepa

Vascepa is a highly purified formulation of only EPA, with each capsule containing one g of icosapent ethyl, which is an ethyl ester EPA. Being EPA, Vascepa is absorbed as described above in Section 2. Plasma and tissue (RBC) exposure to Vascepa is linear with dose (2 and 4 g/day), indicating predictable pharmacokinetics. Demographic factors [age, gender, body weight, body mass index (BMI)], geographic factors (western vs. non-western region), lifestyle factors (self-reported alcohol use and smoking status), and disease factor tested (baseline TG levels, presence of diabetes) did not affect EPA plasma or RBC concentrations. Exposure has not been studied in children or in patients with renal or hepatic impairment.

Drug interaction studies evaluated 4 g of Vascepa per day with omeprazole, rosiglitazone, warfarin, and atorvastatin which are typical substrates of four key cytochrome P450 enzymes involved in the processing of a wide array of chemical compounds. No evidence of drug-drug interactions was observed. As agreed with the FDA, a thorough QT study was not required for Vascepa.

Regarding Vascepa dosing, the MARINE and ANCHOR studies compared 2 and 4 g/day Vascepa with placebo. The selection of 2 and 4 g/day doses for clinical study in hypertriglyceridemia was based upon data from the approvals of EPA and/or omega

acid mixtures containing EPA+DHA that are available in Japan, Europe, and the United States. Safety information was also considered from prior Amarin experience in the CNS development program, which preceded the CV development program. In the Amarin CNS development program, doses ranged from 0.5 g/day to 4 g/day, with the majority of patients receiving 2 g/day; all doses were well tolerated. Of note, in a dose-ranging exploratory study (2 and 4 g/day) of the effects of EPA in patients with persistent schizophrenic symptoms, EPA showed significant reductions in triglyceride levels that had been elevated by clozapine (Peet 2002). Doses larger than 4 g/day (e.g. 8 g/day), require patients to take four capsules twice a day, which was considered impractical and with potential impact on adherence. Dose escalation studies with the omega acid mixture approved for use in the United States showed that doses of 2 g/day did not lower TGs significantly, while 4 g/day provided clinically meaningful reductions in TG. In the same study, 8 g/day provided only modest additional TG lowering above 4g/day. Regarding therapeutic use in various countries, EPA is approved in Japan for the treatment of hyperlipidemia at a dose ranging from 1.8 to 2.7 g/day. In Europe, doses of 1 to 4 g/day of an omega acid mixture are approved for the treatment of hypertriglyceridemia and/or the secondary prevention of post-myocardial infarction (MI) in the period following the initial survival of a heart attack. In the US, Vascepa and an omega acid mixture are both approved for the treatment of severe hypertriglyceridemia at 4 g/day. In consideration of the above data, dosing of 2 and 4 g/day were chosen for study in the MARINE and ANCHOR trials. While the 2 g/day data will be presented, our discussion will primarily focus on the data for 4 g/day.

3.3 Description of Clinical Development program

The Vascepa clinical development program consists of the following studies:

- Two studies conducted in healthy subjects to evaluate pharmacokinetics
- Three drug interaction studies to assess interactions between Vascepa and either omeprazole or rosiglitazone, warfarin, and atorvastatin
- Eight studies in CNS development: Huntington's disease (3 studies), depression (3 studies), schizophrenia (1 study), and age-associated memory impairment (1 study).
- Three randomized placebo-controlled Phase 3 studies in hypertriglyceridemia

In vitro, pharmacokinetic studies were conducted by Amarin, including protein binding, red blood cell partitioning, and metabolism (induction/inhibition) studies. EPA is highly bound to human and animal plasma proteins (~99%) and exhibits low partitioning into erythrocytes. The potential of EPA to induce or inhibit common

Cytochrome P450 (CYP) isoforms was tested in human microsomes. EPA was a weak inhibitor of CYP2C19, CYP2C9, CYP2C8, and to an even lesser extent of CYP2B6 and CYP3A. To further pursue this, clinical drug-drug interaction studies were performed using key utilizers of these pathways, namely omeprazole (CYP2C19), rosiglitazone (CYP2C8), warfarin (CYP2C9), or atorvastatin (CYP3A4); EPA demonstrated no clinically significant effect of Vascepa on the pharmacokinetics of these drugs.

The three randomized, placebo-controlled Phase 3 studies in hypertriglyceridemia are summarized within this Briefing Book. The MARINE study was conducted in patients with very high TG (≥ 500 mg/dL) and was the basis for the initial approval of Vascepa for treatment of severe hypertriglyceridemia. ANCHOR was also a Phase 3 trial, but conducted in patients at high risk for CVD with persistent high fasting TG levels (200 to 499 mg/dL), despite statin treatment to LDL-C goal. REDUCE-IT is an ongoing outcomes trial to evaluate the effect of Vascepa on CV events in patients with high risk for CVD, including high TG, despite statin treatment to LDL-C goal.

3.4 Regulatory History

A pre-IND meeting was held with the FDA on 14 July 2008. At this meeting, Amarin reviewed the design of the Phase 3 studies that would support an indication in patients with both very high (≥ 500 mg/dL) and high triglycerides (200 to 499 mg/dL).

Following the pre-IND meeting, Amarin drafted the first protocol for patients with very high triglycerides (MARINE), received a Special Protocol Assessment agreement from the FDA on 1 May 2009, and submitted the IND to begin this study on 22 May 2009. The results of this study formed the basis for the initial NDA submission on 26 September 2011. The FDA approved Vascepa on 26 July 2012 for the reduction of triglycerides in patients with severe hypertriglyceridemia.

With regard to patients with high triglycerides, the pre-IND meeting discussion resulted in agreement from the FDA regarding study endpoints, choice of placebo, and additional requirements.

Study endpoints

Amarin discussed study design with the FDA and agreed on the following key points:

- Doses of 2 and 4 g/day of Vascepa would be used
- Statin doses should be such that LDL-C is at goal

- The study must rule out a treatment difference of +6% for LDL-C compared to placebo. [The agency stated that this treatment difference is the minimum benefit from doubling a statin dose versus adding a second agent to a regimen.]

On 6 July 2009, Amarin reached agreement with the FDA on a Special Protocol Assessment for the ANCHOR protocol (add-on to statin therapy), including the following additional key design elements:

- The primary endpoint would be the placebo-adjusted percent change in TG from baseline to Week 12.
- The study would enroll patients at high risk for CV disease
- LDL-C at randomization must be between ≥ 40 to <100 mg/dL
- Statin dose must be stable for at least 4 weeks before randomization and must remain constant throughout the 12 week study
- Key secondary endpoints were identified to control for Type 1 error.

The IND was amended to begin the SPA-agreed ANCHOR study.

Although the NDA contained all of the data for ANCHOR, as previously indicated, the FDA did not review the efficacy data at that time.

Choice of Placebo

Corn oil, which had been used as a placebo in other trials of omega 3 polyunsaturated fatty acids, contains triglycerides and has a distinctive yellow color different from icosapent ethyl (colorless). Therefore, Amarin proposed to use light mineral oil, NF, in the placebo capsules for the pivotal studies. The FDA agreed that light mineral oil was acceptable as a placebo as long as the amount per capsule did not exceed the amounts in FDA-approved products given by the same route of administration. Each placebo capsule contained approximately 1 mL of light mineral oil. For the placebo arm, patients were instructed to take two capsules twice daily with food for a maximum total daily consumption of 4 mL/day. Mineral oil has been medically used at higher doses of 15 – 45 mL/day.

Additional requirements

The FDA informed Amarin that in addition to providing results from a 12-week study, an appropriately designed cardiovascular outcomes study would have to be initiated and that at the time of NDA submission for the indication for add-on to statin therapy, approximately half of the patients would need to be enrolled in that outcomes study.

Amarin designed the REDUCE-IT study in collaboration with the FDA and reached SPA agreement on 5 August 2011. The study commenced in November 2011 and reached 50% enrolment by 21 February 2013, at which time the sNDA was submitted to request the addition of the ANCHOR clinical study to the package insert and the indication statement.

REDUCE-IT is a multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study. Patients at high risk for CVD, or with established CVD, with elevated TG (200 to 499 mg/dL) despite optimized statin therapy, are randomized to Vascepa 4 g/day or placebo. The primary endpoint is a composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. The study will require 1612 events to have 90% power to show a 15% reduction in the HR. Approximately 7990 patients will be followed for about 4 years median follow-up. REDUCE-IT is overseen by a Steering Committee and a Data Monitoring Committee.

4. Efficacy Findings in the ANCHOR Trial

4.1 Summary

- The efficacy primary endpoint was the percent change in fasting TG from baseline to 12 weeks with Vascepa as compared to placebo.
 - In the 4 g/day Vascepa arm, the difference from the median placebo percent change from baseline was –21.5 percentage points ($p < 0.0001$). The difference in effect of Vascepa relative to placebo was evident at the 4 week visit and sustained through 12 weeks.
- The non-inferiority primary endpoint was percent change in LDL-C from baseline to 12 weeks with Vascepa as compared to placebo.
 - In the 4 g/day Vascepa arm, the difference from the median placebo percent change from baseline was –6.2 percentage points with an upper bound for the one-sided 97.5% confidence interval of –1.7 percentage points, well below the criterion of +6 percentage point margin used to define inferiority.
- The secondary endpoints were percent change from baseline to Week 12 for: LDL-C, non-HDL-C, VLDL-C, Lp-PLA₂, and Apo B
 - In the 4 g/day Vascepa arm, the difference from the median placebo percent change from baseline was statistically significant (percentage point difference, p-value) for LDL-C (–6.2, $p = 0.0067$), non-HDL-C (–13.6, $p < 0.0001$), VLDL-C (–24.4, $p < 0.0001$), Lp-PLA₂ (–19.0, $p < 0.0001$) and ApoB (–9.3, $p < 0.0001$).
- The exploratory endpoints were percent change from baseline to Week 12 for: TC, HDL-C, VLDL-TG, apo A-1, apo A-1/apo B ratio, Lp(a), LDL particle concentration and size, RLP-C, ox-LDL, and hsCRP. Additional exploratory endpoints included change from baseline to Week 12 for: fasting plasma glucose (FPG) (mg/dL), HbA1c (%), insulin (μ IU/mL), HOMA-IR, ICAM-1 (ng/mL), IL-6 (pg/mL), and PAI-1 (ng/mL). Exploratory endpoints of changes in plasma and RBC EPA concentrations from baseline to Week 12 and change in plasma and RBC concentrations of 28 fatty acids were also evaluated but not summarized in this document.
 - In the 4 g/day Vascepa arm, the difference from the median placebo percent change from baseline was statistically significant (percentage point difference, p-value) for: TC (–12.0, $p < 0.0001$), HDL-C (–4.5, $p = 0.0013$), VLDL-TG (–26.5, $p < 0.0001$), apo A-1 (–2.9, $p < 0.0001$),

LDL particle concentration (-7.7 , $p=0.0017$), particle size ($+0.51$, $p=0.0031$), RLP-C (-25.8 , $p=0.0001$), ox-LDL (-13.3 , $p<0.0001$), and hsCRP (-22.0 , $p=0.0005$).

- In the 4g/day Vascepa arm the following exploratory endpoints comparing percent change from baseline vs. placebo did not meet statistical significance: apo A-1/apo B ratio, and Lp(a).
- In the 4g/day Vascepa arm the following exploratory endpoints comparing change from baseline vs. placebo did not meet statistical significance: FPG, HbA1c, insulin, HOMA-IR, ICAM-1, IL-6, and PAI-1.

4.2 Study Design

ANCHOR was a randomized, double-blind, placebo-controlled Phase 3 study conducted at 97 sites in the US. High risk patients as defined by ATP III entered a 4 to 6 week diet/lifestyle, lipid medication washout, and statin stabilization (for statin-naïve patients) period. At the end of this stabilization period, patients then entered a two week TG and LDL-C qualifying period, during which their fasting TG and LDL-C levels were measured at two weeks prior to randomization and at one week prior to randomization (Visits 2 and 3). LDL-C values for these qualification visits were calculated with the Friedewald equation. After the lipid qualification period, patients entered randomization into a 12 week, double, blind placebo-controlled treatment period. All patients were on a stable statin dose for at least four weeks prior to this two week lipid qualifying period (Figure 1).

The 4 week lead in period for stabilization could be extended by 2 weeks for medication washout. Patients taking non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, dietary supplements or prescription products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects) at the time of screening must have been able to safely discontinue those medications at screening.

In order to enter the 12-week double-blind treatment period, patients must have had a mean fasting LDL-C level ≥ 40 mg/dL and ≤ 115 mg/dL (based on 2 qualifying visits) and fasting TG levels from 2 qualifying visits within the following ranges:

- Mean of the 2 values ≥ 185 mg/dL and at least 1 value ≥ 200 mg/dL and
- Mean of the 2 values < 500 mg/dL.

Inclusion criteria for both TG and LDL-C were modified during trial conduct in a protocol amendment on June 18, 2010 as shown in Table 4. The rationale for modification of entry criteria in the amendment was to facilitate enrollment. A post-

hoc analysis conducted to examine the impact of the protocol amendment (which modified inclusion criteria for TG and LDL-C) found the TG results for both Vascepa 4 g and Vascepa 2 g prior to and after the amendment were similar.

Table 4: Summary of Modifications to Inclusion/Exclusion Criteria in ANCHOR

Criteria Type	Parameter	Original Protocol (before 18 June 2010)	Amended Protocol (after 18 June 2010)
Inclusion	TG	The mean of the 2 values needs to be ≥ 200 mg/dL and < 500 mg/dL	The mean of the 2 values needs to be ≥ 185 mg/dL <u>and</u> at least 1 value needs to be ≥ 200 mg/dL <u>and</u> the mean of the 2 values need to be < 500 mg/dL
Inclusion	LDL-C	The mean of the 2 values needs to be ≥ 40 mg/dL and ≤ 100 mg/dL	The mean of the 2 values needs to be ≥ 40 mg/dL and ≤ 115 mg/dL
Exclusion	HbA1c	HbA1c $> 9.0\%$ at screening	HbA1c $> 9.5\%$ at screening
Exclusion	non-HDL-C	Mean of the 2 values is < 100 mg/dL	

If a patient's LDL-C and/or TG levels from Visit 2 and Visit 3 fell outside the required range for entry into the study, an additional fasting lipid profile could have been collected 1 week later at Visit 3.1 (14-15% of all randomized patients had a Visit 3.1). If a third sample was collected at Visit 3.1, entry into the study was based on the values from Visit 3 and Visit 3.1.

Inclusion and Exclusion Criteria

Males and females at least 18 years of age who were at high risk for CVD and who agreed to maintain a stable diet and exercise program throughout the study were enrolled. High risk for CVD was defined as a 10-year risk $\geq 20\%$, which was based upon the NCEP ATP-III Guidelines. Patients were considered high risk when one of the following criteria was satisfied:

- History of coronary artery disease: one of the following primary criteria needed to be satisfied:
 - History of myocardial infarction,
 - History of unstable or stable angina,

- Previous coronary artery procedures (percutaneous transluminal coronary angioplasty or similar procedures, or coronary artery surgery),
 - Evidence of clinically significant myocardial ischemia;
- Coronary heart disease risk equivalents. One of the following criteria needed to be satisfied:
 - Clinical manifestations of non-coronary forms of atherosclerotic disease: peripheral arterial disease, abdominal aortic aneurysm, or carotid artery disease (transient ischemic attacks or stroke of carotid origin, or >50% obstruction of a carotid artery),
 - Diabetes mellitus (type 1 or 2);

Eligible patients were required to be on a stable dose of statin therapy (with or without ezetimibe). The following criteria must have been satisfied for the concomitant statin therapy:

- The statin must have been atorvastatin, rosuvastatin, or simvastatin;
- The dose of statin must have been stable for ≥ 4 weeks prior to Visit 2 (Week - 2);
- The statin dose must have been optimal such that patients had an LDL-C ≥ 40 mg/dL and ≤ 115 mg/dL based on the qualifying measurements for randomization; and
- The same statin at the same dose must have been continued until the end of the study;

The key exclusion criteria were as follows:

- Body mass index (BMI) > 45 kg/m² at Visit 1
- Hemoglobin A1c $> 9.5\%$ at screening (Visit 1 [Week -8 or Week -6])
- Use after Visit 1 (Week -8 or Week -6) and during the study of any non-study, drug-related, non-statin, lipid-altering medications or supplements including:
 - Niacin > 200 mg daily;
 - Fibrates;
 - Omega-3 fatty acid medications;
 - Dietary supplements containing omega acids or fish oil;

- Supplements (e.g., flaxseed, fish, or algal oils) or foods enriched with
 - omega acids (consumption of up to 2 serving per week of fish was
 - acceptable);
- Sterol/stanol products;
- Dietary fiber supplements, including >2 teaspoons of Metamucil or
 - psyllium-containing supplements per day;
- Red yeast rice supplements, garlic supplements, or soy isoflavones supplements; and
- Any other medications, herbal products, or dietary supplements with known or potential lipid-altering effects;
- Percutaneous coronary intervention within 4 weeks prior to screening (Visit 1 [Week -8 or Week -6]);
- Hospitalization for acute coronary syndrome and discharge within 4 weeks prior to screening (Visit 1 [Week -8 or Week -6])

Study Endpoints

- Primary endpoints:
 - Efficacy endpoint: Percent change in fasting TG from baseline to Week 12 endpoint relative to placebo (to be evaluated for superiority of Vascepa).
 - Non-inferiority endpoint: Non-inferiority evaluation of percent change in LDL-C relative to placebo from baseline to Week 12, with a 6% margin. The 6% margin corresponds with the approximate reduction in LDL-C observed with doubling the dose of a statin.
- Secondary efficacy endpoints: Percent changes in LDL-C, non-HDL-C, VLDL-C, Lp-PLA₂, and Apo B from baseline to Week 12 endpoint as compared to placebo.
- Exploratory efficacy endpoints: Percent changes from baseline in, other lipid parameters (including: TC, HDL-C, VLDL-TG, apo A-I, apo A-I/ apo B, Lp(a), LDL-P number and size, RLP-C, ox-LDL, FPG, HbA1c, insulin, HOMA-IR, ICAM-1, IL-6, PAI-1, hsCRP, plasma and RBC EPA, plasma and RBC content of other omega-3 and -6 fatty acids.

Statistical Methodology

Sample Size Estimation

The sample size required in the ANCHOR study was determined by the prespecified noninferiority comparison of Vascepa versus placebo for percent change from baseline in LDL-C. A sample size of 194 completed patients per treatment arm was projected to provide 80% power to demonstrate non-inferiority ($p < 0.025$, one-sided) of the LDL-C response between Vascepa 4g/day and placebo, with a 6% margin. The 6% margin corresponds with the approximate reduction in LDL-C observed with doubling the dose of a statin. To accommodate a 10% drop-out rate from randomization to completion of the double-blind treatment period, a total of 648 randomized patients was planned (216 patients per treatment arm).

The protocol specified that a 15% difference between Vascepa and placebo was the treatment effect of interest for percent change from baseline in TG. Based upon the 194 patients per treatment arm needed for the noninferiority comparison and assuming a standard deviation of 45%, 194 patients per treatment arm would give 90.6% power to detect a 15% difference (testing at 0.05 significance level).

Statistical Analysis of Primary and Secondary Endpoints

For all primary and secondary endpoints, percent change from baseline was calculated for each patient based upon the following definitions of baseline and ending value. For analysis of TG, baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at one visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing was used as the baseline measurement. Baseline for all other efficacy parameters was the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing was used as the baseline measurement.

The Week 12 endpoint for TG was defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) fasting measurements. If the measurement at one visit was missing, the other visit was used as the endpoint measurement. If the measurements at both visits were missing, the last post-baseline measurement was carried forward (last observation carried forward [LOCF]) as the endpoint measurement. All other efficacy endpoints were measured at Week 0 and Week 12. If the Week 12 value was missing, the last post-baseline measurement was carried forward (LOCF) as the endpoint measurement.

All initial analyses of primary, secondary, and exploratory endpoints relied upon a population definition that is consistent with a modified intent-to-treat (MITT) population. The MITT population included all randomized patients who took at least 1

dose of study drug, had a baseline laboratory efficacy measurement, and had at least 1 post-randomization laboratory efficacy measurement. This SAP definition has the potential to result in bias not consistent with the ITT principle due to between-arm differences in terminations between initiation of study intervention and first evaluation. A mixed model repeated measures (MMRM) analysis was performed to assess this potential bias.

Fifteen randomized patients were excluded from the MITT population for not having any valid lipid measurements post-randomization. Any lipid measurement (TG, TC, HDL-C, LDL-C, non-HDL-C, and VLDL-C) without a recorded fasting status or with a recorded non-fasting status was considered to be invalid. In addition, lipid measurements taken >1 week after the last dose of study drug were also considered to be invalid.

The method of analysis for the primary and secondary endpoints was prespecified as either an analysis of covariance (ANCOVA) model if the data for that endpoint were normally distributed, or a Wilcoxon-rank-sum test if the data were not normally distributed. Significant departure from normality was defined as p-value of <0.01 for the Shapiro-Wilk test.

All primary and secondary endpoints were non-normal in distribution dictating analysis by Wilcoxon-rank-sum testing. Wilcoxon methods were used to compute medians and quartiles were provided for each treatment arm. Hodges-Lehmann estimates for the median of the treatment differences from placebo, and associated 2-tailed 95% confidence intervals, were provided for each treatment comparison.

Noninferiority tests for percent change from baseline in LDL-C were performed between each dose and placebo using a non-inferiority margin of +6 percentage points and a significance level of 0.025.

Closed testing evaluated the difference in the primary TG endpoint between Vascepa doses and placebo. If the Vascepa 4 g/day arm compared to placebo did not reach statistical significance, no testing of Vascepa 2 g/day was to be performed. For secondary endpoints, type 1 error was protected using Hommel-based gatekeeping procedure. Statistical significance was confirmed for all parameters when testing Vascepa 4 g/day arm against placebo before testing Vascepa 2 g/day arm. Sensitivity analyses of the percent change from baseline in fasting TGs were conducted to examine the robustness of the primary analysis.

To examine the impact of premature dropouts, analyses were repeated in the completers with valid Week 11 and/or Week 12 fasting TG values (Week 11 and/or Week 12 without LOCF) to examine the impact due to premature dropouts. A post-hoc analysis using MMRM was conducted to evaluate the robustness of the methods to address missing data, the results of which were consistent with the statistically

significant differences between arms observed in the LOCF analysis.

If any of the baseline values were missing, the remaining values were used to calculate the modified baseline. For any patient, all values used to calculate the modified baseline were from Visit 2 or later and before the first dose of study drug.

4.3 Subject Disposition

Overall, 702 patients were randomized to Vascepa 4 g/day, Vascepa 2 g/day daily or placebo (Table 5). Study completion rates were high in all three treatment arms with reasons for discontinuation well balanced between arms. The ITT population represented a high proportion of the patients randomized in all three treatment arms.

Table 5: Patient Disposition during the Double-Blind Treatment Period in ANCHOR

Category	Placebo (N = 233) n (%)	Vascepa 2 g/day (N = 236) n (%)	Vascepa 4 g/day (N = 233) n (%)
Randomized	233 (100.0)	236 (100.0)	233 (100.0)
ITT population	227 (97.4)	234 (99.2)	226 (97.0)
Completed the study	217 (93.1)	225 (95.3)	221 (94.8)
Early termination from study	16 (6.9)	11 (4.7)	12 (5.2)
Adverse event	7 (3.0)	8 (3.4)	5 (2.1)
Withdrawal of consent	6 (2.6)	2 (0.8)	4 (1.7)
Lost to follow-up	0 (0.0)	1 (0.4)	1 (0.4)
Triglycerides >800 mg/dL	1 (0.4)	0 (0.0)	0 (0.0)
Investigator judgment	0 (0.0)	0 (0.0)	1 (0.4)
Death	1 (0.4)	0 (0.0)	0 (0.0)
Other	1 (0.4)	0 (0.0)	1 (0.4)

Sources: ANCHOR CSR - Tables 14.1.2 and 14.1.3

4.4 Demographics and Baseline Characteristics

The demographic, baseline statin and baseline laboratory characteristics were well balanced between treatment arms (Table 6). Across the three treatment arms, the mean age was 61.4 years and mean BMI was 32.9 kg/m². Simvastatin was the most common HMG-CoA reductase inhibitor used in all arms. TG and LDL-C levels were well balanced within the statin regimens though there were few patients treated with lower statin efficacy regimens.

Table 6: Demographic and Baseline Characteristics in ANCHOR

Characteristic	Placebo (N = 233)	Vascepa 2 g/day (N = 236)	Vascepa 4 g/day (N = 233)
Age, Mean (SD)	61.2 (10.05)	61.8 (9.42)	61.1 (10.03)
Age ≥65 years (%)	37.3	40.3	39.1
Males (%)	62.2	61.0	60.9
White (%)	96.1	95.8	97.0
Weight, kg, Mean (SD)	97.0 (19.14)	95.5 (18.29)	94.5 (18.30)
BMI, Mean (SD)	33.0 (5.04)	32.9 (4.98)	32.7 (4.99)
Type of statin (%)			
Simvastatin	57.1	57.6	57.5
Rosuvastatin	23.6	24.2	23.6
Atorvastatin	19.3	18.2	18.9
Statin efficacy regimen ¹ (n, %)			
Lower potency	15 (6.4)	17 (7.2)	16 (6.9)
Medium potency	144 (61.8)	148 (62.7)	148 (63.5)
Higher potency	74 (31.8)	71 (30.1)	69 (29.6)
Baseline Efficacy Parameters, Mean (SD)			
TG (mg/dL)	270.6 (75.02)	270.2 (72.12)	281.1 (82.88)
LDL-C (mg/dL)	84.6 (19.12)	85.6 (18.76)	85.0 (21.97)
Non-HDL-C (mg/dL)	130.8 (24.40)	131.8 (24.74)	132.2 (25.76)
VLDL-C (mg/dL)	46.3 (17.33)	46.2 (18.50)	47.2 (19.00)
Apo B (mg/dL)	92.8 (16.23)	94.1 (16.46)	94.4 (17.37)
Lp-PLA ₂ (ng/mL)	193.8 (52.99)	194.0 (44.22)	188.9 (46.40)
HDL-C (mg/dL)	39.0 (12.0)	38.0 (13.0)	37.0 (12.0)

¹ Lower potency defined as simvastatin 5-10 mg. Medium potency defined as rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, or simvastatin 10-20 mg + ezetimibe 5-10 mg. Higher potency defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, or simvastatin 40-80 mg + ezetimibe 5-10 mg.

Sources: ANCHOR CSR - Tables 14.1.5 and 14.1.6

Approximately 73% of patients in each treatment arm in ANCHOR had diabetes with many having CVD (Table 7). Concomitant medication use at baseline reflected the high CVD risk of the study patients with a significant prevalence of antidiabetic and CV medication use. Additionally, 83% of study patients had a baseline diagnosis of hypertension, and with a median baseline BMI of 32.4 kg/m², over half of the patients were obese. Those characteristics were similar in all treatment arms.

Table 7: Baseline Medical Characteristics and Concomitant Medication Use in ANCHOR

Characteristic (%)	Placebo (N = 233)	Vascepa 2 g/day (N = 236)	Vascepa 4 g/day (N = 233)
Hypertension	83.7	83.1	82.8
Prior Myocardial Infarction	19.7	14.0	12.4
Prior Angioplasty	23.2	16.9	17.2
Prior CV Bypass	8.6	10.2	9.0
Diabetes*	73.4	72.9	73.4
Diabetes and CVD**	22.9	20.9	18.6
Diabetes without CVD**	49.8	52.1	54.4
Patients on any antidiabetic medication	59.7	58.5	60.5
Platelet inhibitors excluding heparin	60.5	57.2	59.2
Biguanides	41.6	44.9	45.9
ACE inhibitors	33.5	36.9	37.8
Beta-blocking agents, selective	33.5	35.6	30.5
Sulfonamides, urea derivatives	24.0	25.4	25.3
Proton pump inhibitors	24.5	29.7	18.5
Multivitamins, plain	23.2	24.2	22.7

* Incidence in Randomized Population

** Incidence in ITT Population

Sources: ANCHOR CSR - Tables 14.1.9 and 14.1.10

Missing Data

There is no material difference in the likelihood of missing TG data through the end of the study between the placebo and Vascepa arms, and the probability of being missing is less than 10% through the end of the study. Over 90% of the patients have final visits consistent with the timing of the end-of-study (~ 84 days), and no material difference was observed between the control and 4 g/day arms of these estimated probabilities using inverted Kaplan-Meier plots. Thus, descriptive methods failed to find evidence of informative censoring. Other comparisons for the 2 g/day dose and the other primary endpoint of LDL-C are similar.

4.5 Primary Endpoints

Primary Efficacy Endpoint: Percent Change from Baseline in Fasting TG

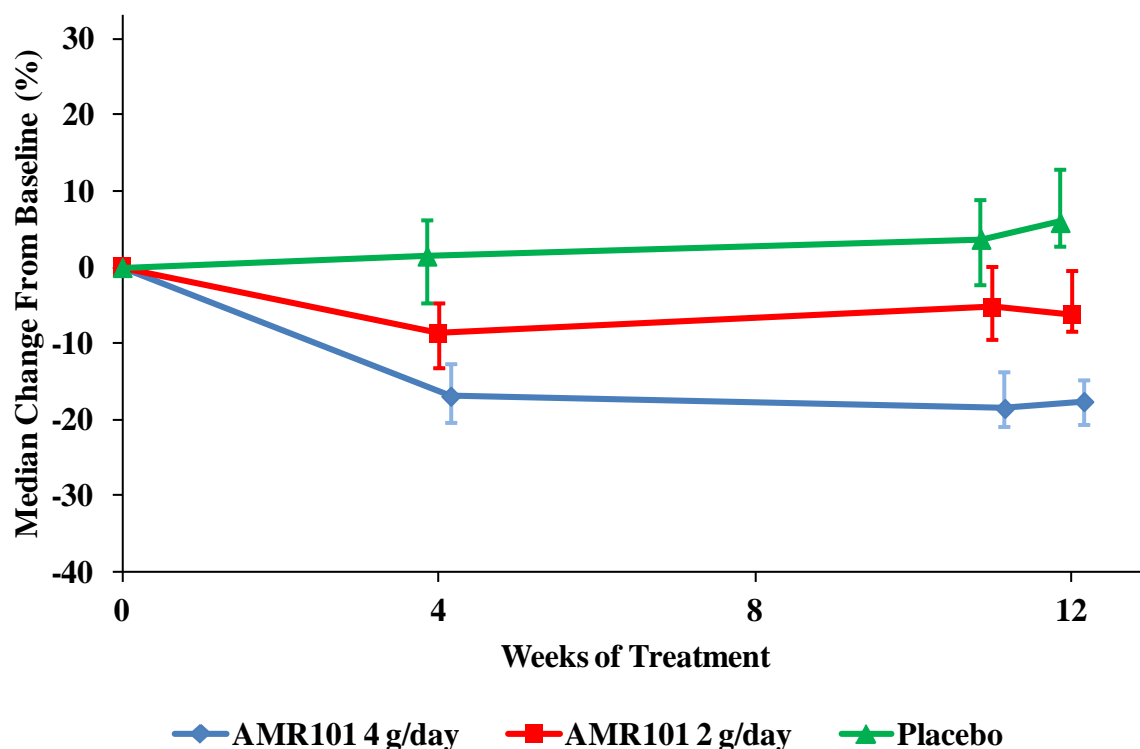
Both doses of Vascepa met the prespecified endpoint of statistically significant reductions in TG compared to placebo (Table 8). The Vascepa arm versus placebo arm difference in median changes for the 12 week outcome was -21.5 percentage points ($p < 0.0001$) for Vascepa 4 g/day and -10.1 percentage points ($p = 0.0005$) for Vascepa 2 g/day. The difference with placebo was observable at 4 weeks and sustained through the end of the study at 12 weeks (Figure 8).

Table 8: Primary Endpoint Analysis in ANCHOR: Percent Change in Fasting TG From Baseline to Week 12 Endpoint

Arm	N	Baseline Median (mg/dL)	Median % Change from Baseline	Estimated Median % Change vs. Placebo (95% CI)	p-value vs. Placebo
Placebo	227	259.0	+5.9 %	--	--
4 g/day	236	264.8	-17.5 %	-21.5% (-26.7, -16.2)	<0.0001
2 g/day	234	254.0	-5.6%	-10.1 (-15.7, -4.5)	0.0005

Sources: ANCHOR CSR - Table 14.2.1

Figure 8: Median Percent Change in Fasting TG at Baseline, Week 4, Week 11 and Week 12



Error bars represent 95% CIs.

Week 0 represents Baseline. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at one visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value.

Week 4 (Visit 5), Week 11 (Visit 6), and Week 12 (Visit 7) measurements include only patients with non-missing values for baseline and the respective timepoint indicated.

Source: ANCHOR CSR Table 14.2.2 and post-hoc analysis 23May2013

Sensitivity Analysis

In patients with valid Week 11 and/or Week 12 fasting TG values (Week 11 and/or Week 12 without LOCF [i.e., completers]), the TG findings were similar to those obtained for the MITT population (LOCF analysis). The estimates of the medians of the treatment differences between the Vascepa 4 g arm and 2 g arm and the placebo arm were -21.8% and -10.7%, respectively.

Mixed Model Repeated Measure (MMRM) statistical modelling was also done as a sensitivity assessment. The model used the base 10 logarithm of fasting triglyceride values as the outcome (logarithm corrects for skewness) and did not impute missing values. The model was parameterised to estimate arm-specific slopes over time with

patients as random effects with random linear coefficients and variance component covariance structure. Thus, the estimated arm-specific slopes are compared statistically. The estimated slope for the 4 g/day arm is negative whereas the estimated slope for the control arm is positive. The slopes are statistically different ($P < 0.0001$). The P value for the slope comparison of the 2 g/day arm to the placebo arm was 0.0259 (graphs not shown).

A post-hoc analysis conducted to examine the impact of the protocol amendment (which modified inclusion criteria for TG and LDL-C) found the TG results for both Vascepa 4 g/day and Vascepa 2 g/day prior to and after the amendment were similar (Table 9).

Table 9: Treatment Differences between Placebo and Vascepa for TG Response Prior to and After Protocol Amendment

Arm (N)	Median Baseline TG (mg/dL)	Estimated Median % Difference vs. Placebo (95% CI)	p-value vs. Placebo
MITT Population			
Placebo (227)	259.0	--	--
4 g/day (226)	264.8	-21.5 (-26.7, -16.2)	<0.0001
2 g/day (234)	254.0	-10.1 (-15.7, -4.5)	0.0005
Prior to Amendment			
Placebo (93)	265.0	--	--
4 g/day (91)	256.0	-19.2 (-27.3, -11.3)	<0.0001
2 g/day (89)	262.5	-9.6 (-18.5, -1.1)	0.0273
After Amendment			
Placebo (134)	250.0	--	--
4 g/day (135)	269.5	-23.0 (-30.0, -15.9)	<0.0001
2 g/day (145)	248.0	-10.5 (-17.8, -2.9)	0.0064

Sources: ANCHOR post-hoc analysis Table TG-amend1, pgm: rpt_nparTGgrp017.sas

4.5.1 Primary Non-Inferiority Endpoint: LDL-C Change Non-Inferiority Assessment

LDL-C was tested for the possibility that Vascepa materially increases LDL-C as compared to placebo. Median percent changes from baseline LDL-C increased in all three treatment arms. This resulted in median percent changes from baseline of +1.5%

($p = 0.1733$) for the Vascepa 4 g/day arm, +2.4% ($p = 0.0010$) for the Vascepa 2 g/day arm, and +8.8% ($p < 0.0001$) for the placebo arm. The respective median changes from baseline to Week 12 were +1.0 mg/dL in the Vascepa 4 g/day arm, +2.0 mg/dL for the Vascepa 2 g/day arm, and +6.5 mg/dL for the placebo arm.

The predefined non-inferiority analysis of LDL-C was based on the between-arm difference in the estimated percent changes. The criterion for rejecting the null hypothesis that inferiority exists (concluding evidence of non-inferiority) is that the upper limits of one-sided 97.5% confidence interval be less than +6 percentage points. In the MITT population, this criterion was met for both 4 and 2 g/day Vascepa versus placebo comparisons (−1.7% and +0.5%, respectively [Table 10]). These results support the conclusion that both doses of Vascepa were non-inferior to placebo. Vascepa 4 g resulted in a median difference from placebo of −6.2% ($p=0.0067$) in LDL-C, while Vascepa 2 g resulted in a median difference of −3.6%.

Table 10: Percent Change in LDL-C (mg/dL) in ANCHOR

Arm	N	Baseline Median	Week 12 Endpoint Median	Percent Change From Baseline	
				Median	Interquartile Range
Placebo	226	84.0	88.5	8.8	(−7.8 , 23.2)
2g/day Vascepa	233	82.0	87.0	2.4	(−8.3 , 17.7)
4 g/day Vascepa	225	82.0	83.0	1.5	(−11.6 , 15.0)
		Arm Difference (Vascepa minus placebo)			
		Estimated Median	95% CI	Non-Inferior	
2 g/day Vascepa vs. placebo		−3.6	(−7.9 , 0.5)	Yes	
4 g/day Vascepa vs. placebo		−6.2	(−10.5 , −1.7)	Yes	

Sources: ANCHOR CSR - Tables 14.2.7

4.6 Secondary Endpoints: Non-HDL-C, VLDL-C, Lp-PLA₂, and Apo B

Both Vascepa doses produced statistically-significant decreases in non-HDL-C, VLDL-C, Lp-PLA₂, and Apo B compared to placebo. In the Vascepa 4 g/day arm there were placebo-adjusted changes of −13.6% in non-HDL-C, −24.4% in VLDL-C, −19.0% in Lp-PLA₂ and −9.3% in Apo B (Table 11). The Vascepa 2 g/day data for these parameters are provided in Table 12 for completeness.

Table 11: Change from Baseline for Non-HDL-C, VLDL-C, Lp-PLA₂ and Apo B in ANCHOR for Vascepa 4 g/day arm compared to the Placebo arm

Endpoint	Vascepa 4 g/day N=226			Placebo N=227			Difference (95% Confidence Interval)	p-value
	n	Baseline	% Change	n	Baseline	% Change		
Non-HDL-C (mg/dL)	226	128	-5.0	227	128	9.8	-13.6 (-17.2, -9.9)	<0.0001
VLDL-C (mg/dL)	225	44	-12.1	226	42	15.0	-24.4 (-31.9, -17.0)	<0.0001
Lp-PLA ₂ (ng/mL)	217	180	-12.8	213	185	6.7	-19.0 (-22.2, -15.7)	<0.0001
Apo B (mg/dL)	217	93	-2.2	219	91	7.1	-9.3 (-12.3, -6.1)	<0.0001

Source: ANCHOR CSR Post-text Tables 14.2.1, 14.2.7, 14.2.9, 14.2.11, 14.2.13, 14.2.15, 14.2.17, 14.2.18, 14.2.19, 14.2.21, 14.2.23, 14.2.35, and 14.2.37

Table 12: Change from Baseline for Non-HDL-C, VLDL-C, Lp-PLA₂ and Apo B in ANCHOR for Vascepa 2 g/day arm compared to Placebo arm

Endpoint	Vascepa 2 g/day N=234			Placebo N=227			Difference (95% Confidence Interval)	p-value
	n	Baseline	% Change	n	Baseline	% Change		
Non-HDL-C (mg/dL)	234	128.0	2.4	227	128	9.8	-5.5 (-9.4, -1.7)	0.0054
VLDL-C (mg/dL)	233	43.0	1.6	226	42	15.0	-10.5 (-18.3, -2.5)	0.0093
Lp-PLA ₂ (ng/mL)	224	190.0	-1.8	213	185	6.7	-8.0 (-11.6, -4.5)	<0.0001
Apo B (mg/dL)	227	91.0	1.6	219	91	7.1	-3.8 (-6.9, -0.7)	0.0170

Sources: ANCHOR CSR Post-text Tables 14.2.1, 14.2.7, 14.2.9, 14.2.11, 14.2.13, 14.2.15, 14.2.17, 14.2.18, 14.2.19, 14.2.21, 14.2.23, 14.2.35, and 14.2.37

4.7 Exploratory Endpoints: Additional Lipid and CV Biomarker Endpoints

Analysis of additional lipid and CV biomarkers, demonstrated significant changes for 4g/day Vascepa versus placebo in TC, HDL-C, hsCRP, ox-LDL, and RLP-C (Table 13), and VLDL-TG (Table 2). The Vascepa 4 g/day endpoint data are presented in Table 13, and the Vascepa 2 g/day endpoint data are provided in Table 14 for

completeness. Both Vascepa doses were associated with a small numerical decrease in HDL-C (Table 2). In addition, statistically significant changes were observed in apo A-1 (-2.9 percentage points for Vascepa 4 g/day compared to placebo, $p < 0.0001$), and in LDL-P concentration and size (Ballantyne 2013). Total LDL-P concentration decreased 7.7 percentage points with Vascepa 4 g/day ($p = 0.0017$) and decreased 7.5 percentage points for Vascepa 2 g/day ($p = 0.0013$), both versus placebo, which was driven by decreases in small LDL-P concentrations (-13.5 percentage points for Vascepa 4g/day ($p < 0.0001$) and -14.7 percentage points for Vascepa 2 g/day ($p < 0.0001$), both compared to placebo). LDL-P size increased with Vascepa 4 g/day (+0.5, $p = 0.0031$) and 2 g/day (+0.5, $p = 0.0007$) compared to placebo. These data support the primary and secondary findings for the Vascepa 4 g/day dose.

Table 13: Change from Baseline for Exploratory Endpoints in ANCHOR for Vascepa 4 g/day arm compared to Placebo arm

Endpoint	Vascepa 4 g/day			Placebo			Difference (%) (95% Confidence Interval)	p-value
	n	Baseline	% Change	n	Baseline	% Change		
TC (mg/dL)	226	167	-3.2	227	168	9.1	-12.0 (-14.9, -9.2)	<0.0001
HDL-C (mg/dL)	226	37	-1.0	227	39	4.8	-4.5 (-7.4, -1.8)	0.0013
hsCRP (mg/L)	217	2.2	-2.4	219	2.2	17.1	-22.0 (-34.1, -9.4)	0.0005
Ox-LDL (U/L)	78	54.0	-4.8	84	51.8	11.6	-13.3 (-19.3, -7.5)	<0.0001
RLP-C (mg/dL)	82	13.5	-24.0	86	14.0	8.0	-25.8 (-39.9, -12.4)	0.0001

ANCHOR CSR Post-text Tables 14.2.1, 14.2.7, 14.2.9, 14.2.11, 14.2.13, 14.2.15, 14.2.17, 14.2.18, 14.2.19, 14.2.21, 14.2.23, 14.2.35, and 14.2.37

Table 14: Change from Baseline for Exploratory Endpoints in ANCHOR for Vascepa 2 g/day arm compared to Placebo arm

Endpoint	Vascepa 2 g/day			Placebo			Difference (%) (95% Confidence Interval)	p-value
	n	Baseline	% Change	n	Baseline	% Change		
TC (mg/dL)	234	169.0	2.1	227	168	9.1	-4.8 (-7.8 , -1.8)	0.0019
HDL-C (mg/dL)	234	38.0	0.0	227	39	4.8	-2.2 (-4.9 , 0.5)	0.1265
hsCRP (mg/L)	234	1.9	10.3	219	2.2	17.1	-6.8 (-20.0,6.0)	0.2889
Ox-LDL (U/L)	75	54.0	2.6	84	51.8	11.6	-5.8 (-11.9,0.9)	0.0946
RLP-C (mg/dL)	84	15.0	-11.1	86	14.0	8.0	-16.7 (-30.0,-3.0)	0.0153

ANCHOR CSR Post-text Tables 14.2.1, 14.2.7, 14.2.9, 14.2.11, 14.2.13, 14.2.15, 14.2.17, 14.2.18, 14.2.19, 14.2.21, 14.2.23, 14.2.35, and 14.2.37

4.8 Prespecified Subgroup Analyses

Primary efficacy (TG) results from subgroup analyses were consistent with the total population. Prespecified subgroups included age group, gender, type of statin used, diabetes status, baseline TG value, and statin efficacy regimen. Statistically significant decreases in TG levels with Vascepa 4 g/day were observed for patients treated with atorvastatin, simvastatin, and rosuvastatin. Analysis by baseline TG tertiles indicated that cohorts with higher baseline TG levels experienced greater TG decreases with Vascepa. Median decreases in TG levels were statistically significant versus placebo and similar in subgroups with and without diabetes mellitus.

Patients with diabetes (73% of the population) were analysed post hoc to assess the effects of Vascepa on median placebo-adjusted percent change from baseline on lipids, lipoproteins, and inflammatory biomarkers based on degree of glycemic control (HbA1c above or below the baseline median of 6.8% in the diabetic cohort). In the diabetic cohort, Vascepa 4 g/day significantly improved many lipid and lipid-related parameters (TG, non-HDL-C, VLDL-C, Lp-PLA₂, Apo B, TC, VLDL-TG, hsCRP, ox-LDL and RLP-C) without worsening glycemic control (no significant effect on FPG, HbA1c, insulin, or HOMA-IR). Additionally, the decreases in TG, non-HDL-C, VLDL-C, Lp-PLA₂, Apo B, TC, VLDL-TG, hsCRP, and Ox-LDL were numerically more pronounced in patients who had less-controlled diabetes at baseline compared with patients who had better-controlled diabetes at baseline. In each of the two diabetes subgroups (above and below the baseline median HbA1c), no statistically significant placebo adjusted changes were observed in the diabetes end points of FPG, HbA1c, HOMA-IR, or insulin following treatment with Vascepa 4 g/day (Brinton 2013). Further discussion of diabetic control will be addressed in the Safety section.

4.9 BMI, Waist Circumference, and Hormone Replacement Therapy

BMI and waist circumference were stable in the MITT population throughout the trial. The use of hormone replacement therapy was low (<4.5%) and evenly distributed across treatment arms. Per protocol, women on hormone replacement therapy were on a stable HRT regimen for ≥ 4 weeks prior to screening and throughout the trial

5. Vascepa Safety

5.1 Summary of Safety Experience with Vascepa

- The Vascepa clinical development program consists of 15 completed studies: 2 Phase 1 studies in healthy subjects; 3 drug interaction studies; 2 Phase 3 clinical studies in the hypertriglyceridemia patient population; and 8 clinical studies in patients with central nervous system (CNS) disorders. The REDUCE-IT study is ongoing.
- The overall safety experience in ANCHOR was generally similar across treatment arms. The incidence of at least 1 treatment emergent adverse event (TEAE) was similar across treatment arms as was AE severity.
- In ANCHOR, AEs were generally similar across treatment arms. AEs occurring at $\geq 1\%$ incidence and numerically greater in the Vascepa 4 g/day arm compared to placebo were arthralgia, dizziness, fatigue, gastroesophageal reflux disease, pain in extremity, peripheral edema, and upper respiratory tract infection.
- The overall SAE incidence was similar across treatment groups. In the Vascepa 4 g/day arm, 3.0% of patients had at least 1 SAE compared to 2.5% in the Vascepa 2 g/day arm and 2.1% in placebo. There was little difference between arms for each specific SAE.
- In ANCHOR, AEs associated with discontinuation were more frequent with placebo than in either Vascepa treatment arm. Specific AEs leading to discontinuation occurred at similar incidence with Vascepa as with placebo.
- In ANCHOR, AEs of interest included those related to gastrointestinal disorders, skin abnormalities, taste perversion, bleeding, and anemia. Other events of interest included hepatic disorders and glucose control.
- The overall Vascepa integrated safety dataset consists of 1683 patients who received Vascepa in either the hypertriglyceridemia clinical studies (N=622) or the CNS studies (N=1,061). This overall Vascepa integrated dataset includes any patient who had been exposed to any dose of Vascepa at the time of the NDA submission, not including healthy subjects. Across the integrated data set of 1683 patients treated with Vascepa, which includes hypertriglyceridemia and CNS patients, the pattern of AEs was generally similar to that observed in MARINE and ANCHOR. The incidence of bleeding-related events was small but greater on Vascepa than placebo. There was no evidence of increased rates of hepatic injury, or adverse skin reactions with Vascepa.

5.2 Safety Experience in ANCHOR

The overall safety experience in ANCHOR was generally similar across treatment

arms (Table 15). The incidence of at least 1 treatment emergent adverse event (TEAE) was similar across treatment arms as was AE severity (classified as mild, moderate or severe). Severe AEs and SAEs occurred at similar incidences in the Vascepa 4 g/day arm as placebo but discontinuation with AEs was more likely in the placebo arm than in either the Vascepa 2 or 4 g/day arms. One death was reported in a patient treated with placebo.

Table 15: Overview of Safety Experience in ANCHOR

Category	Placebo (N = 233) n (%)	Vascepa 2 g/day (N = 236) n (%)	Vascepa 4 g/day (N = 233) n (%)
Patients with at least 1 TEAE	112 (48.1)	106 (44.9)	106 (45.5)
Maximum severity of TEAE			
Mild	58 (24.9)	55 (23.3)	55 (23.6)
Moderate	46 (19.7)	48 (20.3)	42 (18.0)
Severe	8 (3.4)	3 (1.3)	9 (3.9)
Patients with treatment-emergent SAEs	5 (2.1)	6 (2.5)	7 (3.0)
Deaths	1 (0.4)	0 (0.0)	0 (0.0)
Patients with an adverse event leading to discontinuation of study drug	12 (5.2)	8 (3.4)	5 (2.1)
Patients with an SAE leading to discontinuation of study drug	2 (0.9)	0 (0.0)	1 (0.4)

Source: ANCHOR CSR Post-text Table 14.3.1.1

5.2.1 Treatment Emergent Adverse Events in ANCHOR

In ANCHOR, AEs were generally similar across treatment arms. AEs occurring at \geq 1% incidence and numerically greater in the Vascepa 4 g/day arm compared to placebo were arthralgia, dizziness, fatigue, gastroesophageal reflux disease, pain in extremity, peripheral edema, and upper respiratory tract infection (Table 16).

Table 16: TEAEs Occurring in ANCHOR in Any Treatment Arm at $\geq 1\%$ Incidence

Preferred Term	Placebo N=233 n (%)	Vascepa 2 g/day N=236 n (%)	Vascepa 4 g/day N=233 n (%)
Patients With Any AE	112 (48.1)	106 (44.9)	106 (45.5)
Abdominal Distension	3 (1.3)	2 (0.8)	3 (1.3)
Arthralgia	1 (0.4)	8 (3.4)	4 (1.7)
Bronchitis	6 (2.6)	5 (2.1)	2 (0.9)
Diabetes Mellitus	5 (2.1)	4 (1.7)	1 (0.4)
Diarrhea	10 (4.3)	9 (3.8)	8 (3.4)
Dizziness	2 (0.9)	3 (1.3)	4 (1.7)
Fatigue	3 (1.3)	2 (0.8)	4 (1.7)
Flatulence	4 (1.7)	2 (0.8)	3 (1.3)
Gastroesophageal Reflux Disease	2 (0.9)	1 (0.4)	3 (1.3)
Nasopharyngitis	7 (3.0)	6 (2.5)	1 (0.4)
Nausea	7 (3.0)	5 (2.1)	5 (2.1)
Osteoarthritis	0 (0.0)	3 (1.3)	2 (0.9)
Pain	0 (0.0)	4 (1.7)	1 (0.4)
Pain In Extremity	2 (0.9)	1 (0.4)	3 (1.3)
Peripheral Edema	1 (0.4)	5 (2.1)	3 (1.3)
Procedural Pain	0 (0.0)	3 (1.3)	0 (0.0)
Upper Respiratory Tract Infection	5 (2.1)	3 (1.3)	6 (2.6)
Urinary Tract Infection	6 (2.6)	3 (1.3)	6 (2.6)

Source: ANCHOR CSR Post Text 14.3.1.3

5.2.2 Serious Adverse Events in ANCHOR

The overall SAE incidence was similar across treatment arms (Table 17). In the Vascepa 4 g/day arm, 3.0% of patients had at least 1 SAE compared to 2.5% in the Vascepa 2 g/day arm and 2.1% in placebo. There was little difference between arms for each specific SAE. One case of subdural hematoma and one case of subarachnoid hemorrhage were observed on Vascepa treatment in two individuals in ANCHOR. These cases are discussed in more detail in section 5.

Table 17: Treatment Emergent SAEs in ANCHOR by Event

System Organ Class / Preferred Term	Placebo N=233 n (%)	Vascepa 2 g/day N=236 n (%)	Vascepa 4 g/day N=233 n (%)
Patients With Any SAE	5 (2.1)	6 (2.5)	7 (3.0)
Cardiac Disorders	2 (0.9)	2 (0.8)	1 (0.4)
Coronary Artery Disease	1 (0.4)	1 (0.4)	0 (0.0)
Myocardial Infarction	2 (0.9)	0 (0.0)	0 (0.0)
Angina Unstable	0 (0.0)	1 (0.4)	0 (0.0)
Atrioventricular Block Complete	0 (0.0)	0 (0.0)	1 (0.4)
Bradycardia	1 (0.4)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	1 (0.4)	0 (0.0)
Abdominal Pain Upper	0 (0.0)	1 (0.4)	0 (0.0)
General Disorders And Administration Site Conditions	0 (0.0)	2 (0.8)	2 (0.9)
Non-Cardiac Chest Pain	0 (0.0)	2 (0.8)	2 (0.9)
Infections And Infestations	1 (0.4)	0 (0.0)	1 (0.4)
Clostridium Difficile Colitis	1 (0.4)	0 (0.0)	0 (0.0)
Herpes Zoster	0 (0.0)	0 (0.0)	1 (0.4)
Injury, Poisoning And Procedural Complications	0 (0.0)	1 (0.4)	0 (0.0)
Subdural Haematoma	0 (0.0)	1 (0.4)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders	1 (0.4)	0 (0.0)	0 (0.0)
Spondylolisthesis	1 (0.4)	0 (0.0)	0 (0.0)
Neoplasms Benign, Malignant And Unspecified (including Cysts)	1 (0.4)	1 (0.4)	0 (0.0)
Breast Cancer In Situ	0 (0.0)	1 (0.4)	0 (0.0)
Multiple Myeloma	1 (0.4)	0 (0.0)	0 (0.0)
Nervous System Disorders	1 (0.4)	1 (0.4)	2 (0.9)
Subarachnoid Hemorrhage	0 (0.0)	1 (0.4)	1 (0.4)
Lumbar Radiculopathy	1 (0.4)	0 (0.0)	0 (0.0)
Presyncope	0 (0.0)	0 (0.0)	1 (0.4)
Ruptured Cerebral Aneurysm	0 (0.0)	0 (0.0)	1 (0.4)
Syncope	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (0.4)
Chronic Obstructive Pulmonary Disease	0 (0.0)	0 (0.0)	1 (0.4)

Source: ANCHOR CSR Post Text 14.3.1.22

Data listed above is by number of events. A single patient could have more than 1 event.

5.2.3 Adverse Events Associated with Discontinuation in ANCHOR

Discontinuation of study drug due to AEs is shown in Table 18. The most frequent system organ class associated with discontinuation was gastrointestinal disorders which occurred at similar rates across treatment arms.

Table 18: TEAEs in ANCHOR Associated with Discontinuation of Study Drug

System Organ Class / Preferred Term	Placebo N=233 n (%)	Vascepa 2 g/day N=236 n (%)	Vascepa 4 g/day N=233 n (%)
Patients With Any AE Associated with Study Drug Discontinuation	12 (5.2)	8 (3.4)	5 (2.1)
Cardiac Disorders	1 (0.4)	1 (0.4)	0 (0.0)
Myocardial Infarction	1 (0.4)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal Disorders	5 (2.1)	5 (2.1)	4 (1.7)
Diarrhea	1 (0.4)	3 (1.3)	1 (0.4)
Nausea	1 (0.4)	2 (0.8)	0 (0.0)
Abdominal Distension	0 (0.0)	1 (0.4)	0 (0.0)
Abdominal Pain	1 (0.4)	0 (0.0)	0 (0.0)
Abdominal Pain Upper	1 (0.4)	0 (0.0)	0 (0.0)
Gastritis	1 (0.4)	0 (0.0)	0 (0.0)
Gastroesophageal Reflux Disease	0 (0.0)	0 (0.0)	1 (0.4)
Lip Swelling	0 (0.0)	0 (0.0)	1 (0.4)
Esophageal edema	0 (0.0)	1 (0.4)	0 (0.0)
Regurgitation	0 (0.0)	0 (0.0)	1 (0.4)
Infections And Infestations	1 (0.4)	0 (0.0)	0 (0.0)
Herpes Zoster	1 (0.4)	0 (0.0)	0 (0.0)
Musculoskeletal And Connective Tissue Disorders	0 (0.0)	2 (0.8)	0 (0.0)
Bursitis	0 (0.0)	1 (0.4)	0 (0.0)
Muscle Spasms	0 (0.0)	1 (0.4)	0 (0.0)
Rheumatoid Arthritis	0 (0.0)	1 (0.4)	0 (0.0)
Neoplasms Benign, Malignant And Unspecified	1 (0.4)	0 (0.0)	0 (0.0)
Multiple Myeloma	1 (0.4)	0 (0.0)	0 (0.0)
Nervous System Disorders	1 (0.4)	1 (0.4)	1 (0.4)
Brain Edema	0 (0.0)	0 (0.0)	1 (0.4)
Dizziness	0 (0.0)	1 (0.4)	0 (0.0)
Headache	1 (0.4)	0 (0.0)	0 (0.0)
Ruptured Cerebral Aneurysm	0 (0.0)	0 (0.0)	1 (0.4)
Subarachnoid Hemorrhage	0 (0.0)	0 (0.0)	1 (0.4)
Psychiatric Disorders	1 (0.4)	1 (0.4)	0 (0.0)
Listless	0 (0.0)	1 (0.4)	0 (0.0)
Nightmare	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders	1 (0.4)	0 (0.0)	0 (0.0)
Throat Tightness	1 (0.4)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	1 (0.4)	0 (0.0)	0 (0.0)
Rash	1 (0.4)	0 (0.0)	0 (0.0)

Source: ANCHOR CSR Post Text 14.3.1.23

5.2.4 Adverse Events of Interest in ANCHOR

In ANCHOR adverse events of interest included those related to gastrointestinal

disorders, skin abnormalities, taste perversion, bleeding, and anemia that have been previously reported by patients taking omega-3 fatty acids. Other events of interest included hepatic disorders and glucose control.

The incidence of diarrhea and nausea were similar in the treatment arms (Table 19). Only 1 patient (in the Vascepa 4 g/day arm) reported the TEAE of dysgeusia (taste perversion). The incidence of flatulence, constipation, eructation, and abdominal pain was lower in the Vascepa treatment arms than the placebo arm. Three (0.4%) patients had the TEAE of anemia: two (0.9%) patients in the Vascepa 4 g/day arm and one (0.4%) patient in the Vascepa 2 g/day arm. The incidence of pruritus was higher in the placebo arm (1.7%) than in the Vascepa arms (0.4% in each arm). All other preferred terms of TEAEs of interest were experienced by three or fewer patients.

Table 19: Summary of TEAEs of Interest in ANCHOR by System Organ Class

System Organ Class Preferred term	Placebo (N = 233) n (%)	Vascepa 2 g/day (N = 236) n (%)	Vascepa 4 g/day (N = 233) n (%)	Total (N = 702) n (%)
Blood and lymphatic system disorders	0 (0.0)	3 (1.3)	3 (1.3)	6(0.9)
Anemia	0 (0.0)	1 (0.4)	2 (0.9)	3 (0.4)
Spontaneous hematoma	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	40 (17.2)	27 (11.4)	27 (11.6)	94 (13.4)
Diarrhea	10 (4.3)	9 (3.8)	8 (3.4)	27 (3.8)
Nausea	7 (3.0)	5 (2.1)	5 (2.1)	17 (2.4)
Flatulence	4 (1.7)	2 (0.8)	3 (1.3)	9 (1.3)
Abdominal distention	3 (1.3)	2 (0.8)	3 (1.3)	8 (1.1)
Constipation	4 (1.7)	2 (0.8)	2 (0.9)	8 (1.1)
Abdominal pain	4 (1.7)	2 (0.8)	1 (0.4)	7 (1.0)
Eructation	4 (1.7)	1 (0.4)	2 (0.9)	7 (1.0)
Gastroesophageal reflux disease	2 (0.9)	1 (0.4)	3 (1.3)	6 (0.9)
Abdominal pain upper	1 (0.4)	2 (0.8)	2 (0.9)	5 (0.7)
Abdominal discomfort	2 (0.9)	0 (0.0)	1 (0.4)	3 (0.4)
Dyspepsia	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Vomiting	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Hematochezia	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.3)
Regurgitation	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Abdominal pain lower	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Abdominal tenderness	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Duodenitis	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Feces hard	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Gastritis	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Gastritis erosive	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Nervous system disorders	13 (5.6)	11 (4.7)	11 (4.7)	35 (5.0)
Dysgeusia	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Skin and subcutaneous tissue disorders	10 (4.3)	7 (3.0)	10 (4.3)	27 (3.8)
Pruritus	4 (1.7)	1 (0.4)	1 (0.4)	6 (0.9)
Dermal cyst	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Rash	1 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Rash pruritic	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.3)
Dermatitis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Drug eruption	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Dyshidrosis	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Petechiae	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Rash erythematous	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Rash maculo-papular	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Rosacea	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Skin ulcer	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Urticaria	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Note: A TEAE was defined as an adverse event that occurred for the first time on or after the first dose date, or existed prior to dosing and worsened during the double-blind treatment period. TEAE = treatment-emergent adverse event. Source: ANCHOR CSR: Post-text Table 14.3.1.2				

5.2.5 Incidence of Bleeding in ANCHOR

In the ANCHOR study, incidence of bleeding-related AEs was low in all treatment arms, but occurred more often on Vascepa (2.4%) than on placebo (1.3%). To evaluate any potential risk with Vascepa, the AE database was searched for all bleeding-related AEs occurring during the treatment period. A total of 19 bleeding-related AEs occurring in 17 patients (15 (2.8%) on Vascepa and 4 (1.7%) on placebo) were identified (Table 20).

Two of the 19 events were major bleeding events that occurred in the setting of co-morbid conditions. One case of subdural hematoma occurred in a 72 year old female with a history of ethanol abuse who was randomized to Vascepa 2 g/day. She had an alcohol related syncopal episode and a fall leading to a head injury 21 days after her last dose of Vascepa. Brain imaging confirmed a subarachnoid bleed and subdural hematoma. A second case was reported in a 49 year old female with a history of hypertension (BP 140/82 at randomization) randomized to 4 g/day of Vascepa who developed a severe headache on day 66 of Vascepa treatment. On presentation she had severely uncontrolled high blood pressure (measurement unavailable). Brain imaging and arteriography revealed a subarachnoid hemorrhage due to a ruptured anterior communicating artery aneurysm.

Table 20: Summary of ALL Bleeding TEAEs by Preferred Term during the Double-Blind Treatment Period – Safety Population (ANCHOR)

Preferred term	Placebo (N = 233) n (%)	Vascepa 2 g/day (N = 236) n (%)	Vascepa 4 g/day (N = 233) n (%)	Total (N = 702) n (%)
Anemia	0 (0.0)	1 (0.4)	2 (0.9)	3 (0.4)
Spontaneous hematoma	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Hematochezia	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.1)
Contusion	2 (0.9)	2 (0.8)	0 (0.0)	4 (0.6)
Hematoma	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Infusion Site Hematoma	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Subarachnoid Hemorrhage	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.1)
Subdural Hematoma	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Traumatic Hematoma	0 (0.0)	1 (0.4)	2 (0.9)	3 (0.4)
Uterine Hemorrhage	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Total Events	4	9	6	19
Total number of Patients with any event	4 (0.2)	7 (0.3)	6 (0.3)	17 (0.2)

Source: ANCHOR CSR post-text 14.3.1.2

Bleeding-related AEs in ANCHOR were also examined within the subgroup of patients treated with antiplatelet and anticoagulant use. Overall, 59% of patients on Vascepa and 57% on placebo received concomitant antiplatelet therapy during the treatment period. Aspirin was the most frequent reported medication in all treatment arms. In total, 405 (57.4%) patients in the randomized population were taking aspirin at a median daily dose of 81 mg (Table 21). Each treatment arm included about the same proportion (55-59%) of patients on aspirin. All 405 patients took aspirin for the full duration of the 12-week double-blind treatment period.

Table 21: Summary of Daily Doses of Aspirin (mg) in Patients Taking Aspirin in ANCHOR

Statistic	Placebo	Vascepa 2 g/day	Vascepa 4 g/day	Overall
n	138	131	136	405
Mean, mg (SD)	139 (115)	135 (105)	146 (107)	140 (109)
Median	81	81	81	81
Min - Max	81 - 650	81 - 650	46 - 325	46 – 650

Source: ANCHOR post hoc analysis 07 June 2013

Across ANCHOR, 18 patients including 10 on placebo and 8 on Vascepa were treated with warfarin, 3 patients, (2 on Vascepa and 1 on placebo) were treated with enoxaparin and 1 patient on placebo received unfractionated heparin (UFH) concomitantly during the trial. Of these patients, there were two bleeding-related events. One event was the subarachnoid haemorrhage with Vascepa 2 g. The other event was a localized hematoma that occurred with placebo in the patient treated with UFH.

To evaluate the effect of Vascepa on laboratory measures that may signal an increased bleeding risk, Amarin conducted study LA01.01.0009 in healthy subjects to evaluate bleeding time. This was a Phase 1, multiple-dose, clinical pharmacology/PK study in healthy male volunteer subjects. An investigation of skin bleeding time was performed pre-dose and 6 hours after dosing on Days 1 - 3 and Days 30 – 32. All subjects had values within the reference range of 150 to 570 seconds, and there were no important differences between the Vascepa and placebo treatment arms. Overall, there was no clinically important effect of Vascepa treatment on skin bleeding time. Amarin also conducted a drug interaction study with warfarin in 25 healthy volunteers. Study 0021 showed that when administered together with warfarin, Vascepa did not alter INR or PT.

Doses of omega acid mixtures in excess of 3 g/day have been linked with an increase

in bleeding time (FDA 1997). The Norwegian Food Safety Report found that bleeding time increased after intake of 6.9 g/day of the mixture in CHD patients on anti-coagulation therapy. However there were no adverse bleeding complications seen up to that dose and a clear upper intake level associated with bleeding could not be established.

Comprehensive evaluation of available data (Harris 2007, Mozaffarian 2012) suggests that these concerns may not reflect the true risk of bleeding with omega fatty acid therapy. In a review of 19 trials of subjects taking 3 to 6 g of omega acid mixtures, it was shown that the risk for bleeding was not elevated compared to subjects not taking omega acid mixtures. (Harris 2007) Of those trials, 13 were studies ranging in size from n=30 to n=814. The subjects were pre-treated with omega acid mixtures at up to 6 g/day for up to 42 days and then underwent percutaneous transluminal coronary angioplasty (PTCA). These subjects received post-procedure anti-platelet therapy. Review of the data showed that bleeding was not an issue in the majority of the trials. In one trial with n = 242, 4 events of bleeding were reported in the treated group, including 2 events at puncture sites, one with heme-positive stool event and one with GI bleed requiring transfusion. Two trials in patients undergoing CABG requiring use of large amount of heparin intra-operatively and anticoagulation measures post-operatively did not reveal any bleeding events. Mozaffarian et al (2012) reported on the OPERA trial which sought to evaluate whether 1 g of an omega acid mixture reduces postoperative atrial fibrillation (AF) in patients undergoing cardiac surgeries. Compared with patients in the placebo group, those in the omega acid mixture group received significantly fewer packed red blood cell transfusions, including during surgery (p=0.002), after surgery (p= 0.008), and overall (p=0.001). Other bleeding indices did not significantly differ by treatment. In a retrospective review of bleeding, Watson et al (Watson 2009) found that patients on dual anti-platelet therapy (ASA+clopidogrel) had no difference in bleeding than patients on dual anti-platelet therapy plus omega acid mixtures (ASA+clopidogrel+omega acid mixtures).

Overall, bleeding-related events were low across the Vascepa development program but more common on Vascepa than on placebo. In light of inconsistent data with omega acid mixtures and bleeding, we recommend that patients at higher risk for bleeding events should be clinically monitored periodically.

5.2.6 Hepatic Disorders in ANCHOR

Five patients in ANCHOR experienced hepatic disorders characterized by ALT >3x ULN, AST >3x ULN, and CK >5x ULN at any time during the double-blind treatment period were low. No patients exceeded values of ALT >5x ULN and AST >5x ULN during the double-blind treatment period. For completeness, the data for all these cut-

off limits are listed in Table 22. No patient's lab values met the criteria for Hy's Law. None of the five patients experienced elevations of alkaline phosphatase and bilirubin. Patient 037-008 experienced a slight elevation of alkaline phosphatase at all visits including at Visit 1 (baseline), while bilirubin was normal. All values for alkaline phosphatase and bilirubin were normal in the 4 other patients.

Table 22: Summary of Defined ALT, AST and Creatine Kinase Changes in ANCHOR

Parameter	Abnormality Criteria	Placebo (N=233) n/N' (%)	VASCEPA 2 g/day (N=236) n/N' (%)	VASCEPA 4 g/day (N=233) n/N' (%)	Overall (N=702) n/N' (%)
ALT	>3x ULN	1/227 (0.4)	0/232 (0.0)	2/227 (0.9)	3/686 (0.4)
	>5x ULN	0/227 (0.0)	0/232 (0.0)	0/227 (0.0)	0/686 (0.0)
AST	>3x ULN	1/227 (0.4)	0/232 (0.0)	0/227 (0.0)	1/686 (0.1)
	>5x ULN	0/227 (0.0)	0/232 (0.0)	0/227 (0.0)	0/686 (0.0)
CK	>5x ULN	1/227 (0.4)	1/232 (0.4)	0/227 (0.0)	2/686 (0.3)
	>10x ULN	0/227 (0.0)	0/232 (0.0)	0/227 (0.0)	0/686 (0.0)

%=n/N', where n is the number of patients with specified abnormality and N' is the number of patients with records. Source: ANCHOR CSR Table 14.3.4.13

5.2.7 Glucose Control in ANCHOR

There was an increase with Vascepa in FPG at 12 weeks compared to baseline. The changes in FPG from baseline were small, not statistically significant, and similar between placebo and 2 g/day dose (Table 24). The changes in FPG from baseline were higher in the Vascepa 4g/day arm (8.9 mg/dL) compared to placebo (4.2 mg/dL) (Table 23). Among patients with diabetes, changes in FPG from baseline were also higher in the 4 g/day arm (11 mg/dL) compared to placebo (5 mg/dL). To determine if the changes in FPG are representative of altered glucose metabolism, a review of changes from baseline fasting insulin levels, HbA1c, and HOMA-IR was conducted; there were no differences observed between Vascepa 2 or 4 g/day and placebo.

During the study, patients with diabetes generally remained on a stable anti-diabetic treatment regimen with only 2.9% of patients in the Vascepa 4 g/day arm requiring an increase in their anti-diabetic treatment. This was comparable to placebo (3.5%). There were two cases (patient 016-034 and patient 049-040) of AE's of new onset diabetes in the Vascepa 4 g/day arm. Both patients represent a reclassification of glycemic status rather than new diagnoses as both had elevated HbA1c and FPG at baseline but were

counted in the “no-diabetes group” as they did not report a history of diabetes at screening.

Overall, Vascepa demonstrated no deleterious effect on glucose control as compared to the placebo arm in ANCHOR, as evidenced by a lack of clinically meaningful changes with either dose. Post-hoc analysis in the diabetic subgroup (73% of total population) exhibited results similar to the overall study population. There were no statistically significant changes in fasting plasma glucose, HbA1c, insulin or HOMA-IR (Brinton 2013). However FPG in the Vascepa 4g/day showed a numerically greater increase from baseline to 12 weeks compared to placebo and Vascepa 2 g/day.

The totality of the ANCHOR data including change from baseline HbA1c, HOMA-IR, and fasting plasma glucose and fasting plasma insulin suggests that Vascepa is unlikely to significantly alter glucose metabolism.

Table 23: Change from Baseline for Fasting Plasma Glucose, HbA1c, and Insulin in ANCHOR for Vascepa 4 g/day arm compared to Placebo arm

Parameter	Vascepa 4 g/day N=226			Placebo N=227			Difference (95% Confidence Interval)	p-value
	n	Baseline	LS Mean Change	n	Baseline	LS Mean Change		
FPG mg/dL	217	133.1	8.9	219	128.9	4.2	4.7 (-1.2, 10.6)	0.1200
HbA1c %	220	6.6	0.3	218	6.5	0.2	0.1 (-0.1,0.2)	0.0899
Insulin μIU/mL	215	19.6	-1.1	215	23.0	-1.2	0.0 (-2.5,2.5)	0.99

ANCHOR CSR Post-text Tables 14.2.39-44

Table 24: Change from Baseline for Fasting Blood Glucose, HbA1c, and Insulin in ANCHOR for Vascepa 2 g/day compared to Placebo

Parameter	Vascepa 2 g/day N=234			Placebo N=227			Difference (%) (95% Confidence Interval)	p-value
	n	Baseline	LS Mean Change	n	Baseline	LS Mean Change		
FBG mg/dL	226	134.8	3.6	219	128.9	4.2	-0.6 (-6.5, 5.3)	0.8408
HbA1c (%)	228	6.7	0.2	218	6.5	0.2	0.0 (-0.1,0.1)	0.9392
Insulin μIU/mL	217	18.6	-1.2	215	23.0	-1.2	-0.1 (-2.6,2.4)	0.9567

ANCHOR CSR Post-text Tables 14.2.39-44

5.2.8 ECG Changes in ANCHOR

In ANCHOR, 6 patients on Vascepa had QTcB (Bazett's correction) increase from baseline ≥ 60 ms, ranging from 60 – 104 ms. None were discontinued from study medication. Patient 103-025 with the longest prolongation (104 ms), reported an AE of supraventricular tachycardia and atrial fibrillation. This patient is a 67 year old male with diabetes and hypertension randomized to 2 g/day of Vascepa. He had a normal ECG at screening but abnormal at the week-12 visit. His concomitant medications included Glimepiride 2 mg, Lexapro, Pravastatin 40, Multivitamin, Zithromax, Dilacor XL, Benazepril/HCL, pioglitazone and metformin. QtcB was 412 ms at baseline and 516 ms at Week 12. At visit 6 visit, the patient was diagnosed with tachycardia with a heart rate of 128 BPM. No ECG is available. Study medication was not stopped. At the same visit, adverse events of supraventricular tachycardia and premature ventricular complexes were reported by the investigator. At the next visit his heart rate was 95 BPM.

5.3 Integrated ANCHOR and MARINE Safety Experience

The incidence of TEAEs was similar in the Vascepa (45.8%) and placebo arm (48.9%). All individual TEAEs were reported at a low frequency.

Serious AEs were reported in 18 Vascepa patients (2.9%) and in 5 placebo patients (1.6%). (Table 25). The most common SAEs reported in the pooled Vascepa group (n=622) were non-cardiac chest pain (Vascepa, 0.8%; placebo, 0%), coronary artery disease (Vascepa, 0.3%; placebo, 0.3%), and subarachnoid hemorrhage (Vascepa,

0.3%; placebo, 0%). No other SAEs were reported by more than one Vascepa patient. Two placebo patients (0.6%), and no Vascepa patients, experienced myocardial infarction.

Table 25: Serious AEs by System Organ Class in ANCHOR and MARINE

System Organ Class Preferred Term	Placebo Pooled N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa Daily Dose (Pooled)	
			2 g/day N=312 n (%)	4 g/day N=310 n (%)
Any System Organ Class	5 (1.6)	18 (2.9)	9 (2.9)	9 (2.9)
Cardiac Disorders	2 (0.6)	5 (0.8)	2 (0.6)	3 (1.0)
Coronary Artery Disease	1 (0.3)	2 (0.3)	1 (0.3)	1 (0.3)
Angina Unstable	0	1 (0.2)	1 (0.3)	0
Atrioventricular Block Complete	0	1 (0.2)	0	1 (0.3)
Cardiac Failure Congestive	0	1 (0.2)	0	1 (0.3)
Bradycardia	1 (0.3)	0	0	0
Myocardial Infarction	2 (0.6)	0	0	0
General Disorders and Administration Site Conditions	0	5 (0.8)	3 (1.0)	2 (0.6)
Non-Cardiac Chest Pain	0	5 (0.8)	3 (1.0)	2 (0.6)
Nervous System Disorders	1 (0.3)	3 (0.5)	1 (0.3)	2 (0.6)
Subarachnoid Hemorrhage	0	2 (0.3)	1 (0.3)	1 (0.3)
Presyncope	0	1 (0.2)	0	1 (0.3)
Ruptured Cerebral Aneurysm	0	1 (0.2)	0	1 (0.3)
Syncope	0	1 (0.2)	1 (0.3)	0
Lumbar Radiculopathy	1 (0.3)	0	0	0
Gastrointestinal Disorders	0	1 (0.2)	1 (0.3)	0
Abdominal Pain Upper	0	1 (0.2)	1 (0.3)	0
Infections and Infestations	1 (0.3)	1 (0.2)	0	1 (0.3)
Herpes Zoster	0	1 (0.2)	0	1 (0.3)
Clostridium Difficile Colitis	1 (0.3)	0	0	0
Injury, Poisoning and Procedural Complications	0	1 (0.2)	1 (0.3)	0
Subdural Hematoma	0	1 (0.2)	1 (0.3)	0
Metabolism and Nutrition Disorders	0	1 (0.2)	1 (0.3)	0
Diabetes Mellitus	0	1 (0.2)	1 (0.3)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.3)	1 (0.2)	1 (0.3)	0
Arthralgia	0	1 (0.2)	1 (0.3)	0

System Organ Class Preferred Term	Placebo Pooled N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa Daily Dose (Pooled)	
			2 g/day N=312 n (%)	4 /day N=310 n (%)
Spondylolisthesis	1 (0.3)	0	0	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	1 (0.3)	1 (0.2)	1 (0.3)	0
Breast Cancer in Situ	0	1 (0.2)	1 (0.3)	0
Multiple Myeloma	1 (0.3)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.2)	0	1 (0.3)
Chronic Obstructive Pulmonary Disease	0	1 (0.2)	0	1 (0.3)
<p>The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.</p> <p>A patient with multiple AEs within a primary SOC is counted only once in the total row.</p> <p>Treatment-emergent SAEs include those that first occurred or worsened after the first dose of study drug and occurred within 30 days of study drug discontinuation.</p> <p>Source: ISS Summary Table ISS.HT.6.2-1</p>				

5.3.1 Treatment Emergent Adverse Events Leading to Discontinuation in ANCHOR and MARINE

TEAEs leading to discontinuation during double-blind treatment in the MARINE and ANCHOR integrated dataset are listed below (Table 26). The incidence of patients reporting TEAEs leading to discontinuation was 2.3% for the Vascepa pooled group, compared to 3.2% of the placebo group. The most common TEAE leading to discontinuation in the Vascepa pooled group in this population was diarrhea (Vascepa, 0.8%; placebo, 0%), followed by nausea (Vascepa, 0.3%; placebo, 0.6%). The remaining TEAEs were not reported in more than one Vascepa patient.

Table 26: TEAEs Leading to Discontinuation in ANCHOR and MARINE

System Organ Class Preferred Term	Placebo Pooled N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa Daily Dose (Pooled)	
			2 g N=312 n (%)	4 g N=310 n (%)
Any System Organ Class	10 (3.2)	14 (2.3)	9 (2.9)	5 (1.6)
Gastrointestinal Disorders	4 (1.3)	10 (1.6)	6 (1.9)	4 (1.3)
Diarrhea	0	5 (0.8)	4 (1.3)	1 (0.3)
Nausea	2 (0.6)	2 (0.3)	2 (0.6)	0
Abdominal Distention	0	1 (0.2)	1 (0.3)	0
Gastroesophageal Reflux Disease	0	1 (0.2)	0	1 (0.3)
Lip Swelling	0	1 (0.2)	0	1 (0.3)
Esophageal Edema	0	1 (0.2)	1 (0.3)	0
Regurgitation	0	1 (0.2)	0	1 (0.3)
Abdominal Pain	1 (0.3)	0	0	0
Gastritis	1 (0.3)	0	0	0
Musculoskeletal and Connective Tissue Disorders	1 (0.3)	2 (0.3)	2 (0.6)	0
Bursitis	0	1 (0.2)	1 (0.3)	0
Muscle Spasms	0	1 (0.2)	1 (0.3)	0
Rheumatoid Arthritis	0	1 (0.2)	1 (0.3)	0
Arthralgia	1 (0.3)	0	0	0
Nervous System Disorders	1 (0.3)	2 (0.3)	1 (0.3)	1 (0.3)
Brain Edema	0	1 (0.2)	0	1 (0.3)
Dizziness	0	1 (0.2)	1 (0.3)	0
Ruptured Cerebral Aneurysm	0	1 (0.2)	0	1 (0.3)
Subarachnoid Hemorrhage	0	1 (0.2)	0	1 (0.3)
Headache	1 (0.3)	0	0	0
Cardiac Disorders	0	1 (0.2)	1 (0.3)	0
Palpitations	0	1 (0.2)	1 (0.3)	0
Psychiatric Disorders	1 (0.3)	1 (0.2)	1 (0.3)	0
Listless	0	1 (0.2)	1 (0.3)	0
Nightmare	1 (0.3)	0	0	0
Metabolism and Nutrition Disorders	1 (0.3)	0	0	0
Gout	1 (0.3)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.3)	0	0	0
Throat Tightness	1 (0.3)	0	0	0
Skin and Subcutaneous Tissue Disorders	1 (0.3)	0	0	0
Rash	1 (0.3)	0	0	0

AEs = adverse events; SOC = system organ class.
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
The table includes AEs with “Adverse Event” as the primary reason for withdrawal. Source: [ISS Summary Table ISS.HT.6.3-1](#)

5.3.2 Treatment Emergent Adverse Events by Patient Subgroup in ANCHOR and MARINE

No meaningful differences were noted in the profile of TEAEs experienced in ANCHOR and MARINE in the subgroups of gender, age, race, smoking status, or alcohol use. The incidence of patients reporting TEAEs was greater in patients receiving concomitant statins (47.6%) compared to those not taking concomitant statins (39.7%)(Table 27).

Table 27: TEAEs by Concomitant Medication Use (Statin Therapy) in ANCHOR and MARINE

System Organ Class Preferred Term	Placebo Pooled N=309		Vascepa Pooled N=622	
	On Statin n=235 n (%)	No Statin n=74 n (%)	On Statin n=481 n (%)	No Statin n=141 n (%)
Any System Organ Class	124 (52.8)	27 (36.5)	229 (47.6)	56 (39.7)
Infections and Infestations	42 (17.9)	9 (12.2)	67 (13.9)	9 (6.4)
Gastrointestinal Disorders	48 (20.4)	12 (16.2)	58 (12.1)	17 (12.1)
Musculoskeletal and Connective Tissue Disorders	11 (4.7)	6 (8.1)	38 (7.9)	11 (7.8)
Respiratory, Thoracic and Mediastinal Disorders	11 (4.7)	2 (2.7)	21 (4.4)	9 (6.4)
General Disorders and Administration Site Conditions	7 (3.0)	5 (6.8)	24 (5.0)	5 (3.5)
Injury, Poisoning and Procedural Complications	6 (2.6)	4 (5.4)	21 (4.4)	7 (5.0)
Nervous System Disorders	12 (5.1)	4 (5.4)	24 (5.0)	4 (2.8)
Investigations	5 (2.1)	0	24 (5.0)	3 (2.1)
Skin and Subcutaneous Tissue Disorders	13 (5.5)	3 (4.1)	19 (4.0)	5 (3.5)
Metabolism and Nutrition Disorders	10 (4.3)	2 (2.7)	20 (4.2)	2 (1.4)
Vascular Disorders	5 (2.1)	1 (1.4)	9 (1.9)	9 (6.4)
Cardiac Disorders	7 (3.0)	0	8 (1.7)	2 (1.4)
Psychiatric Disorders	2 (0.9)	1 (1.4)	8 (1.7)	2 (1.4)
Blood and Lymphatic System Disorders	0	0	6 (1.2)	3 (2.1)
Eye Disorders	3 (1.3)	2 (2.7)	5 (1.0)	3 (2.1)
Ear and Labyrinth Disorders	1 (0.4)	2 (2.7)	6 (1.2)	1 (0.7)
Reproductive System and Breast Disorders	3 (1.3)	0	2 (0.4)	5 (3.5)
Renal and Urinary Disorders	5 (2.1)	0	4 (0.8)	2 (1.4)
Neoplasms, Benign, Malignant and Unspecified	4 (1.7)	0	3 (0.6)	1 (0.7)
Hepatobiliary Disorders	1 (0.4)	0	2 (0.4)	0
Endocrine Disorders	0	0	2 (0.4)	0
Immune System Disorders	2 (0.9)	0	1 (0.2)	0

Source: ISS Summary Table ISS.HT.SGP.1-4

Hypertriglyceridemia patients with type 2 diabetes treated with Vascepa tended to have a greater incidence of TEAEs (49.0%) compared to patients without diabetes treated with Vascepa (40.9%). However, the rate of TEAEs in patients with type 2 diabetes treated with Vascepa (49.0%) was slightly lower than that of patients with type 2 diabetes treated with placebo (54.1%) (Table 28).

Table 28: TEAEs Occurring in 2% or More Patients in Any Diabetes (Safety Analysis Set) in ANCHOR and MARINE

System Organ Class Preferred Term	PlaceboPooled N=309 ¹		Vascepa Pooled N=622 ¹	
	Type 2 n=194	Non-Diabetics n=115	Type 2 n=386	Non-Diabetics n=235
Any System Organ Class	105 (54.1)	46 (40.0)	189 (49.0)	96 (40.9)
Infections and Infestations	36 (18.6)	15 (13.0)	58 (15.0)	18 (7.7)
Urinary Tract Infection	9 (4.6)	3 (2.6)	12 (3.1)	2 (0.9)
Upper Respiratory Tract Infection	4 (2.1)	2 (1.7)	10 (2.6)	3 (1.3)
Bronchitis	5 (2.6)	3 (2.6)	5 (1.3)	3 (1.3)
Nasopharyngitis	5 (2.6)	3 (2.6)	7 (1.8)	0
Gastrointestinal Disorders	41 (21.1)	19 (16.5)	49 (12.7)	26 (11.1)
Diarrhea	12 (6.2)	5 (4.3)	16 (4.1)	7 (3.0)
Nausea	10 (5.2)	2 (1.7)	9 (2.3)	7 (3.0)
Abdominal Pain	5 (2.6)	0	3 (0.8)	1 (0.4)
Constipation	4 (2.1)	0	3 (0.8)	1 (0.4)
Eructation	2 (1.0)	6 (5.2)	3 (0.8)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	12 (6.2)	5 (4.3)	31 (8.0)	18 (7.7)
Arthralgia	3 (1.5)	1 (0.9)	8 (2.1)	8 (3.4)
Pain in Extremity	1 (0.5)	3 (2.6)	6 (1.6)	2 (0.9)
Muscle Spasm	4 (2.1)	1 (0.9)	2 (0.5)	0
General Disorders and Administration Site Conditions	7 (3.6)	5 (4.3)	14 (3.6)	15 (6.4)
Fatigue	4 (2.1)	1 (0.9)	4 (1.0)	3 (1.3)
Nervous System Disorders	12 (6.2)	4 (3.5)	21 (5.4)	7 (3.0)
Headache	4 (2.1)	0	1 (0.3)	2 (0.9)
Skin and Subcutaneous Tissue Disorders	13 (6.7)	3 (2.6)	12 (3.1)	12 (5.1)
Pruritus	4 (2.1)	1 (0.9)	1 (0.3)	2 (0.9)
Metabolism and Nutrition Disorders	8 (4.1)	4 (3.5)	18 (4.7)	4 (1.7)
Diabetes Mellitus	5 (2.6)	0	6 (1.6)	0
Vascular Disorders	6 (3.1)	0	9 (2.3)	9 (3.8)
Hypertension	3 (1.5)	0	4 (1.0)	5 (2.1)
¹ There were no type 1 diabetics in the placebo group and one type 1 diabetic in the Vascepa pooled group; there were no TEAEs reported for the type 1 diabetic in the Vascepa pooled group. AEs = adverse events; SOC = system organ class. The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with multiple AEs within a primary SOC is counted only once in the total row. Source: ISS Summary Table ISS.HT.SGP.1-7				

5.3.3 Laboratory Evaluation in ANCHOR and MARINE

In analysis of chemistry, hematology and urinalysis laboratory data, there were no significant differences between Vascepa treatment groups and placebo in change from

baseline to Week 12 endpoint for any laboratory endpoint. Shift table analysis also did not indicate any difference between Vascepa and placebo.

Analysis of possibly clinically significant (PCS) findings at any time post baseline did not suggest any effect of Vascepa on any hematology (Table 29) or chemistry parameters (Table 30). Importantly because a significant proportion of patients were treated with statins, there was no difference in the proportion of patients with PCS values for creatinine kinase between treatment groups.

Table 29: Treatment-Emergent Potentially Clinically Significant Hematology Laboratory Results at any Time Post-Baseline in MARINE and ANCHOR Integrated Dataset

Parameter	Abnormality	Criterion	Placebo Pooled N=309 n/N (%)	Vascepa Pooled N=622 n/N (%)	Vascepa Daily Dose Pooled	
					2 g/day N=312 n/N (%)	4 g/day N=310 n/N (%)
Erythrocytes	PCS Low	Female: ≤ 3.5 ($\times 10^6/\mu\text{L}$)	2/103 (1.9)	1/212 (0.5)	0/106	1/106 (0.9)
		Male: ≤ 3.8 ($\times 10^6/\mu\text{L}$)	0/194	1/387 (0.3)	0/195	1/192 (0.5)
	PCS High	Female: > 5.5 ($\times 10^6/\mu\text{L}$)	0/103	1/212 (0.5)	0/106	1/106 (0.9)
		Male: > 6.0 ($\times 10^6/\mu\text{L}$)	0/194	0/387	0/195	0/192
Hemoglobin	PCS Low	≤ 10.0 (g/dL)	1/297 (0.3)	0/599	0/301	0/298
	PCS High	Female: > 16.5 (g/dL)	0/103	0/212	0/106	0/106
		Male: > 18.0 (g/dL)	0/194	2/387 (0.5)	1/195 (0.5)	1/192 (0.5)
Leukocytes	PCS Low	≤ 1.5 ($\times 10^3/\mu\text{L}$)	0/297	0/599	0/301	0/298
Platelets	PCS Low	≤ 100 ($\times 10^3/\mu\text{L}$)	1/294 (0.3)	1/585 (0.2)	1/295 (0.3)	0/290
	PCS High	≥ 500 ($\times 10^3/\mu\text{L}$)	0/294	0/585	0/295	0/290

LLN = lower limit of normal; PCS = potentially clinically significant; ULN = upper limit of normal.
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug. A treatment-emergent PCS high value is defined as a change from a baseline value that is \leq ULN to a post-baseline PCS value. A treatment-emergent PCS low value is defined as a change from a baseline value that is \geq LLN to a post-baseline PCS value.
PCS categories, which had no patients that met the criteria, were not included within this in-text table.
Source: [ISS Summary Table ISS.HT.7.2-6](#)

5.3.4 Events of Special Interest in ANCHOR and MARINE

Bleeding

Bleeding in ANCHOR was previously discussed, in MARINE there were no SAEs related to bleeding and other bleeding related events were similar in nature and frequency for Vascepa and placebo.

Hepatic Disorders

Overall 1.1% of Vascepa patients experienced hepatic disorders compared to 1.3% of placebo. None of the hepatic disorders met the regulatory definition of serious. The most common TEAE of this category was alanine aminotransferase (ALT) increased in 4 patients (0.6%) (Table 30). Three of these 4 patients TEAEs (hepatic enzyme increased, hepatic steatosis, and liver function test abnormal) led to discontinuation of treatment. None of the cases met the criteria for Hy's rule (ALT >3 x the upper limit of normal [ULN] and bilirubin >2 x ULN). One patient (097-009) in ANCHOR treated with Vascepa 4 g/day had normal baseline ALT with a change of ALT value >3 times the ULN on treatment. This patient's ALT was 36 U/L at randomization. On Study Day 87 (one day after the last dose of study treatment), the ALT value was 163 U/L. The ALT decreased to 73 U/L 12 days later. His concomitant medications included simvastatin and lisinopril/hydrochlorothiazide. His bilirubin was not elevated.

Glucose Control

Glucose control in ANCHOR was previously discussed. In MARINE there were minimal, non- statistically significant changes in glucose control. Changes from baseline to Week 12 in HbA1c were minimal (–0.1% to 0.1%) across all treatment arms. The other parameters of glucose control including FPG, fasting plasma insulin, and HOMA-IR showed minimal and balanced changes across arms.

Table 30: Treatment-Emergent Potentially Clinically Significant Chemistry Laboratory Results at any Time Post-Baseline in ANCHOR and MARINE Integrated Dataset

Parameter	Abnormality/Criterion	Placebo Pooled N=309 n/N (%)	Vascepa Pooled N=622 n/N (%)	Vascepa Daily Dose Pooled	
				2 g N=312 n/N (%)	4 g N=310 n/N (%)
ALT	PCS High:				
	>1 x ULN to 2 x ULN	24/234 (10.3)	60/467 (12.8)	26/231 (11.3)	34/236 (14.4)
	>3 x ULN	0/234	1/467 (0.2)	0/231	1/236 (0.4)
ALP	PCS High:				
	>1 x ULN to 2 x ULN	13/288 (4.5)	10/576 (1.7)	6/291 (2.1)	4/285 (1.4)
AST	PCS High:				
	>1 x ULN to 2 x ULN	31/256 (12.1)	61/506 (12.1)	29/256 (11.3)	32/250 (12.8)
Bilirubin	PCS High:				
	>1 x ULN to 2 x ULN	1/294 (0.3)	9/595 (1.5)	7/300 (2.3)	2/295 (0.7)
BUN	PCS High:				
	≥31 mg/dL	2/301 (0.7)	2/607 (0.3)	2/304 (0.7)	0/303
Calcium	PCS Low:				
	≤7 mg/dL	0/301	1/607 (0.2)	1/304 (0.3)	0/303
Creatine Kinase	PCS High:				
	1 x ULN to 5 x ULN	22/241 (9.1)	43/510 (8.4)	18/255 (7.1)	25/255 (9.8)
Creatinine	PCS Low:				
	Female: <0.5 mg/dL	2/103 (1.9)	10/213 (4.7)	6/106 (5.7)	4/107 (3.7)
	Male: <0.65 mg/dL	8/198 (4.0)	23/394 (5.8)	18/198 (9.1)	5/196 (2.6)
Glucose	PCS High:				
	≥130 mg/dL	10/301 (3.3)	16/603 (2.7)	4/302 (1.3)	12/301 (4.0)
Potassium	PCS High:				
	≥5.5 mEq/L	4/301 (1.3)	0/603	0/303	0/300
Sodium	PCS Low:				
	≤130 mEq/L	1/301 (0.3)	4/607 (0.7)	2/304 (0.7)	2/303 (0.7)
ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; LLN = lower limit of normal; PCS = potentially clinically significant; ULN = upper limit of normal Source: ISS Summary Table ISS.HT.7.1-6					

5.4 Overall Vascepa Integrated Dataset

The Vascepa clinical development program consists of 2 Phase 1 studies in healthy subjects, 3 drug interaction studies, 2 Phase 3 clinical studies in the hypertriglyceridemia patient populations, and 8 clinical studies in patients with central nervous system (CNS) disorders. Across the clinical development program, of the 1683 adults who were treated with Vascepa, not including healthy volunteers, 1478 adults were treated with 2 or 4 g/day of Vascepa. The remaining 205 patients received either 0.5 or 1 mg/day of Vascepa.

Treatment emergent AEs in the 1683 patients treated with Vascepa in development were similar to those observed in ANCHOR. The most common TEAEs in the Vascepa pooled group were diarrhea (6.4%), depression (3.7%), falls (3.7%), and nausea (3.3%). No dose-related trends were observed. The TEAEs of depression and falls primarily occurred in the CNS studies. These TEAEs were reported at a similar rate to placebo (Vascepa 4.1% versus placebo 3.9% for depression, and Vascepa 3.9% versus placebo 3.1% for falls).

AEs leading to discontinuation were also similar. The overall incidence of patients reporting TEAEs leading to discontinuation was 2.9% with Vascepa (all Vascepa experience). There were no TEAEs leading to discontinuation reported in 1.0% or more Vascepa patients. The most common TEAE leading to discontinuation in the Vascepa pooled group was diarrhea (0.5%), followed by nausea (0.3%) and psychotic disorder (0.2%).

The SAEs reported are summarized in Table 31. Of the 1683 patients treated with Vascepa, 75 patients (4.5%) reported at least 1 SAE. The most common SAEs reported by patients taking Vascepa were non-cardiac chest pain (0.3%), aggression (0.2%), depression (0.2%), psychotic disorder (0.2%), overdose (0.2%), irritability (0.2%), and coronary artery disease (0.2%). There were no dose related trends. Two cases of subarachnoid hemorrhage and 2 cases of subdural haematoma were reported with Vascepa and described earlier in the ANCHOR safety section.

Table 31: Serious Adverse Events in the Overall Vascepa Integrated Dataset

System Organ Class Preferred Term	All Vascepa N=1683 n(%)	Vascepa Daily Dose			
		0.5 g N=19 n(%)	1 g N=186 n(%)	2 g N=1100 n(%)	4 g N=378 n(%)
Any System Organ Class	75 (4.5)	0	8 (4.3)	56 (5.1)	11 (2.9)
Psychiatric Disorders	19 (1.1)	0	1 (0.5)	16 (1.5)	2 (0.5)
Aggression	3 (0.2)	0	0	3 (0.3)	0
Depression	3 (0.2)	0	0	3 (0.3)	0
Psychotic Disorder	3 (0.2)	0	1 (0.5)	2 (0.2)	0
Paranoia	2 (0.1)	0	0	2 (0.2)	0
Suicidal Ideation	2 (0.1)	0	0	2 (0.2)	0
Affective Disorder	1 (0.1)	0	0	1 (0.1)	0
Completed Suicide	1 (0.1)	0	0	1 (0.1)	0
Depressive Symptom	1 (0.1)	0	0	0	1 (0.3)
Disturbance in Social Behavior	1 (0.1)	0	0	0	1 (0.3)
Impulse-Control Disorder	1 (0.1)	0	0	1 (0.1)	0
Intermittent Explosive Disorder	1 (0.1)	0	0	1 (0.1)	0
Major Depression	1 (0.1)	0	0	1 (0.1)	0
Mental Disorder	1 (0.1)	0	0	1 (0.1)	0
Mood Altered	1 (0.1)	0	0	1 (0.1)	0
Injury, Poisoning and Procedural Complications	13 (0.8)	0	3 (1.6)	10 (0.9)	0
Overdose	3 (0.2)	0	2 (1.1)	1 (0.1)	0
Fall	2 (0.1)	0	0	2 (0.2)	0
Subdural Hematoma	2 (0.1)	0	0	2 (0.2)	0
Ankle Fracture	1 (0.1)	0	0	1 (0.1)	0
Comminuted Fracture	1 (0.1)	0	1 (0.5)	0	0
Femoral Neck Fracture	1 (0.1)	0	0	1 (0.1)	0
Road Traffic Accident	1 (0.1)	0	0	1 (0.1)	0
Subdural Hemorrhage	1 (0.1)	0	0	1 (0.1)	0
Wrist Fracture	1 (0.1)	0	0	1 (0.1)	0
General Disorders and Administration Site Condition	11 (0.7)	0	0	9 (0.8)	2 (0.5)
Non-Cardiac Chest Pain	5 (0.3)	0	0	3 (0.3)	2 (0.5)
Irritability	3 (0.2)	0	0	3 (0.3)	0
Condition Aggravated	1 (0.1)	0	0	1 (0.1)	0
Drug Withdrawal Syndrome	1 (0.1)	0	0	1 (0.1)	0
Pyrexia	1 (0.1)	0	0	1 (0.1)	0
Nervous System Disorders	9 (0.5)	0	0	7 (0.6)	2 (0.5)
Subarachnoid Hemorrhage	2 (0.1)	0	0	1 (0.1)	1 (0.3)
Cerebrovascular Accident	1 (0.1)	0	0	1 (0.1)	0

System Organ Class Preferred Term	All Vascepa N=1683 n(%)	Vascepa Daily Dose			
		0.5 g N=19 n(%)	1 g N=186 n(%)	2 g N=1100 n(%)	4 g N=378 n(%)
Extrapyramidal Disorder	1 (0.1)	0	0	1 (0.1)	0
Grand Mal Convulsion	1 (0.1)	0	0	1 (0.1)	0
Ischemic Stroke	1 (0.1)	0	0	1 (0.1)	0
Migraine	1 (0.1)	0	0	1 (0.1)	0
Motor Dysfunction	1 (0.1)	0	0	1 (0.1)	0
Presyncope	1 (0.1)	0	0	0	1 (0.3)
Ruptured Cerebral Aneurysm	1 (0.1)	0	0	0	1 (0.3)
Syncope	1 (0.1)	0	0	1 (0.1)	0
Cardiac Disorders	7 (0.4)	0	0	4 (0.4)	3 (0.8)
Coronary Artery Disease	3 (0.2)	0	0	2 (0.2)	1 (0.3)
Angina Unstable	1 (0.1)	0	0	1 (0.1)	0
Atrioventricular Block Complete	1 (0.1)	0	0	0	1 (0.3)
Cardiac Failure Congestive	1 (0.1)	0	0	0	1 (0.3)
Myocardial Infarction	1 (0.1)	0	0	1 (0.1)	0
Infections and Infestations	4 (0.2)	0	0	3 (0.3)	1 (0.3)
Bacterial Infection	1 (0.1)	0	0	1 (0.1)	0
Helicobacter Gastritis	1 (0.1)	0	0	1 (0.1)	0
Herpes Zoster	1 (0.1)	0	0	0	1 (0.3)
Pneumonia	1 (0.1)	0	0	1 (0.1)	0
Metabolism and Nutrition Disorders	4 (0.2)	0	1 (0.5)	3 (0.3)	0
Cachexia	1 (0.1)	0	0	1 (0.1)	0
Decreased Appetite	1 (0.1)	0	1 (0.5)	0	0
Diabetes Mellitus	1 (0.1)	0	0	1 (0.1)	0
Water Intoxication	1 (0.1)	0	0	1 (0.1)	0
Musculoskeletal and Connective Tissue Disorders	4 (0.2)	0	3 (1.6)	1 (0.1)	0
Arthralgia	2 (0.1)	0	1 (0.5)	1 (0.1)	0
Back Pain	1 (0.1)	0	1 (0.5)	0	0
Neck Pain	1 (0.1)	0	1 (0.5)	0	0
Gastrointestinal Disorders	2 (0.1)	0	0	2 (0.2)	0
Abdominal Pain Upper	1 (0.1)	0	0	1 (0.1)	0
Fecaloma	1 (0.1)	0	0	1 (0.1)	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	2 (0.1)	0	0	2 (0.2)	0
Breast Cancer in Situ	1 (0.1)	0	0	1 (0.1)	0
Lung Neoplasm Malignant	1 (0.1)	0	0	1 (0.1)	0
Reproductive System and Breast Disorders	2 (0.1)	0	0	2 (0.2)	0
Benign Prostatic Hyperplasia	1 (0.1)	0	0	1 (0.1)	0

System Organ Class Preferred Term	All Vascepa N=1683 n(%)	Vascepa Daily Dose			
		0.5 g N=19 n(%)	1 g N=186 n(%)	2 g N=1100 n(%)	4 g N=378 n(%)
Prostatomegaly	1 (0.1)	0	0	1 (0.1)	0
Blood and Lymphatic System Disorders	1 (0.1)	0	0	1 (0.1)	0
Iron Deficiency Anemia	1 (0.1)	0	0	1 (0.1)	0
Hepatobiliary Disorders	1 (0.1)	0	0	1 (0.1)	0
Cholelithiasis	1 (0.1)	0	0	1 (0.1)	0
Immune System Disorders	1 (0.1)	0	0	1 (0.1)	0
Allergy to Arthropod Sting	1 (0.1)	0	0	1 (0.1)	0
Investigations	1 (0.1)	0	0	1 (0.1)	0
Endoscopy	1 (0.1)	0	0	1 (0.1)	0
Renal and Urinary Disorders	1 (0.1)	0	0	1 (0.1)	0
Urinary Retention	1 (0.1)	0	0	1 (0.1)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1)	0	0	0	1 (0.3)
Chronic Obstructive Pulmonary Disease	1 (0.1)	0	0	0	1 (0.3)
Vascular Disorders	1 (0.1)	0	0	1 (0.1)	0
Arterial Occlusive Disease	1 (0.1)	0	0	1 (0.1)	0

Of the 1683 patients treated with Vascepa, there were 2 deaths: a completed suicide in a Huntington's disease patient taking Vascepa 2 g/day and an accidental dothiepin overdose in a CNS patient taking Vascepa 1 g/day.

Occurrences of bleeding were distributed throughout all treatment groups in all populations, and the data do not suggest an excess occurrence of bleeding tendency with Vascepa (Table 32). A comprehensive discussion on bleeding and Vascepa can be found in section 5. Overall, subdural hematoma, subdural hemorrhage, and subarachnoid hemorrhage were rare and reported in 0.1% of Vascepa. The cases in ANCHOR were discussed above. The cases in the CNS program are added below. All cases of subdural hematoma were preceded by a fall or head injury. Note that one of these events was coded to fall and not subdural hematoma. Contusions occurred in both the placebo and active treatment groups. In the healthy subjects integrated dataset, all of the bruising events were due to venipuncture. The rate of contusion was identical for the active treatment and placebo groups (0.6%). In the CNS placebo-controlled integrated dataset, the rate of contusion was similar for Vascepa pooled (0.7%) compared to placebo (0.6%).

A 35-year-old Caucasian male with Huntington's disease on Vascepa 2g/day fell during a skiing holiday. No apparent injury was sustained at that time, but on return from holiday he developed a headache. Four days later he became aggressive and complained of

headache. He was admitted to hospital where a brain scan revealed a subdural hemorrhage (hematoma), which was considered severe in intensity.

A 73-year-old Caucasian male with Huntington's disease complained of a headache and eye pain 160 days after starting Vascepa 2g/day. He felt shaky and his balance had worsened. He developed a headache and was admitted to the hospital. Three weeks prior to the hospitalization, he had fallen, hitting his head, fracturing his wrist and suffering a laceration above his right eyebrow. On admission to the hospital, a CT scan revealed a subdural hematoma, which was considered to be secondary to the fall, and severe in nature.

A 47-year-old Caucasian male with Huntington's disease on placebo fell and sustained a head injury on Day 34. Several days after the fall, the patient developed right-sided paresis. and was subsequently admitted to the hospital. A CT scan revealed a subdural hematoma, which was considered to be severe in nature.

53-year-old male patient with Huntington's disease on Vascepa 2 g/day suffered a subdural hematoma following a fall approximately 10 months after the start of study medication.

No clinically meaningful findings were observed for laboratory or vital sign results. The occurrences of liver disorder were similar to ANCHOR. There have been no cases reported of increases in ALT or AST concomitant with a 2 fold or more increase in bilirubin. Although no formal ECG studies were conducted to evaluate Vascepa treatment, observed changes in ECG parameters as part of the safety evaluation including (QTcF) ≥ 30 milliseconds (ms) or ≥ 60 ms were generally small and similar in both the placebo and Vascepa groups.

Table 32: Treatment-Emergent Adverse Events Possibly Related to Bleeding Tendency (Safety Analysis Set)

TEAE Preferred Term Studies	CNS Placebo-Controlled Integrated Dataset Double-Blind		Hypertriglyceridemia Placebo-Controlled Integrated Dataset Double-Blind		Overall Vascepa Integrated Dataset Double-Blind and Open-Label
	Placebo Pooled N=519 n(%)	Vascepa Pooled N=700 n(%)	Placebo Pooled N=309 n(%)	Vascepa Pooled N=622 n(%)	Vascepa Pooled N=1683 n(%)
Anemia	0	3 (0.4)	0	5 (0.8)	11 (0.7)
Bleeding Time Prolonged	0	1 (0.1)	0	0	1 (0.1)
Conjunctival Hemorrhage	0	1 (0.1)	0	0	1 (0.1)
Contusion	3 (0.6)	5 (0.7)	2 (0.6)	4 (0.6)	11 (0.7)
Dysfunctional Uterine Bleeding	0	0	0	0	1 (0.1)
Ecchymosis	0	1 (0.1)	0	0	1 (0.1)
Epistaxis	1 (0.2)	0	0	0	1 (0.1)
Hematochezia	0	0	1 (0.3)	1 (0.2)	2 (0.1)
Hematocrit Abnormal	0	0	0	0	1 (0.1)
Hematoma	1 (0.2)	0	0	1 (0.2)	3 (0.2)
Hematoma Infection	0	0	0	0	1 (0.1)
Hematuria	1 (0.2)	0	0	0	1 (0.1)
Hemoglobin Decreased	2 (0.4)	0	0	0	2 (0.1)
Hemorrhagic Diathesis	0	0	0	1 (0.2)	1 (0.1)
Hemorrhage	0	0	0	0	1 (0.1)
Hemorrhoidal Hemorrhage	1 (0.2)	0	0	0	0
Increased Tendency to Bruise	0	0	1 (0.3)	1 (0.2)	2 (0.1)
Infusion Site Hematoma	0	0	1 (0.3)	0	0
Iron Deficiency Anemia	0	1 (0.1)	0	0	2 (0.1)
Mouth Hemorrhage	0	0	1 (0.3)	0	0
Post Procedural Hemorrhage	0	1 (0.1)	0	0	1 (0.1)
Postmenopausal Hemorrhage	1 (0.2)	1 (0.1)	0	0	1 (0.1)
Rectal Hemorrhage	1 (0.2)	0	0	0	0
Spontaneous Hematoma	0	0	0	1 (0.2)	1 (0.1)
Subarachnoid Hemorrhage	0	0	0	2 (0.3)	2 (0.1)
Subdural Hematoma	1 (0.2)	1 (0.1)	0	1 (0.2)	2 (0.1)
Subdural Hemorrhage	0	1 (0.1)	0	0	1 (0.1)
Traumatic Hematoma	0	0	0	3 (0.5)	3 (0.2)
Uterine Hemorrhage	0	0	0	1 (0.2)	1 (0.1)
Vaginal Hemorrhage	1 (0.2)	2 (0.3)	0	0	4 (0.2)

AE = adverse event; TEAE = treatment emergent adverse event. The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment. Source: ISS Summary Tables ISS.CNS.6.1-1, ISS.HT.6.1-1, and ISS.O.6.1-1

Generally, the AE profile was similar among all of the Vascepa safety populations, with gastrointestinal AEs being among the most common complaints. Serious events were rare and usually balanced. Bleeding was rare but numerically greater on Vascepa. In conclusion, the data provided within this section indicate that Vascepa is safe and well-tolerated.

Table 33 summarizes all potential cases of hepatic injury reported in the 1683 patients treated with Vascepa in clinical development. None of the events were considered serious, with 3 (hepatic enzyme increased, hepatic steatosis, and liver function test abnormal) leading to discontinuation of treatment (0.1% each). There were no cases meeting the criteria for Hy's Law (ALT >3x ULN and bilirubin >2x ULN).

Table 33: Hepatic Disorders Observed in the Overall Vascepa Integrated Dataset

System Organ Class Preferred Term	Vascepa Pooled N=1683 n (%)	Vascepa Daily Dose (pooled)			
		0.5 g N=19 n (%)	1 g N=186 n (%)	2 g N=1100 n (%)	4 g N=378 n (%)
Possibly Treatment-Related Hepatic Disorders, Any Preferred Term	20 (1.2)	0	1 (0.5)	17 (1.5)	2 (0.5)
ALT Increased	7 (0.4)	0	1 (0.5)	4 (0.4)	2 (0.5)
AST Increased	4 (0.2)	0	0	3 (0.3)	1 (0.3)
GGT Increased	3 (0.2)	0	0	3 (0.3)	0
Hepatic Enzyme Increased	3 (0.2)	0	0	3 (0.3)	0
Hepatic Steatosis	3 (0.2)	0	0	2 (0.2)	1 (0.3)
Blood Alkaline Phosphatase Increased	2 (0.1)	0	0	2 (0.2)	0
Liver Function Test Abnormal	2 (0.1)	0	0	2 (0.2)	0
ALT Abnormal	1 (0.1)	0	0	1 (0.1)	0
AST Abnormal	1 (0.1)	0	0	1 (0.1)	0
Chronic Hepatitis	1 (0.1)	0	0	1 (0.1)	0
GGT Abnormal	1 (0.1)	0	0	1 (0.1)	0
Source: ISS Summary Table ISS.O.HEP.1-1					

6. Benefit and Risk Discussion and Conclusion

Many patients retain a high cardiovascular (CV) risk despite achieving their recommended LDL-C targets. Based on a series of large statin trials, optimal statin treatment reduces CVD events by 30-40% over five years (Cannon 2007, Cholesterol Treatment Trialists' 2008), meaning many patients treated to LDL-C goal still have residual CVD risk. An important independent contributor to this residual risk is elevated non-high density lipoprotein cholesterol (non-HDL-C), which is often driven by elevated hepatic TG. A growing body of evidence supports TG as an important biomarker of CV risk (Austin 2000, Austin 1998, Assmann 1996, Sarwar 2007).

After diet and lifestyle modification, and after reaching LDL-C goal, if a patient has persistently elevated TG (≥ 200 mg/dL), ATP III recommends a secondary treatment goal for non-HDL-C. TG-lowering therapies are key therapeutic options for the reduction of non-HDL-C in this hypertriglyceridemic patient population.

Current TG-lowering therapies, including fibrates, niacin, and omega acid mixtures limitations. These limitations contribute to a high rate of treatment discontinuation within the first year of therapy (Abughosh 2004).

- Increase in LDL-C

Fibrates, the prescription omega acid mixture (Lovaza), dietary supplements containing omega acid mixtures, and other marine oils, can all increase LDL-C (Jacobson 2012).

- Myopathy and Contraindications in Liver Disease

Fibrates and niacin may increase the risk for myopathy as monotherapy and this risk is increased when combined with statins. Fibrates and niacin also include contraindications in liver disease.

- Contraindications in Gallbladder and Renal Disease

Fibrates additionally include contraindications in gallbladder and renal disease.

- Worsening Glycemic Control and Flushing

Niacin may worsen glycemic control in diabetic patients and causes flushing in many patients, which may interfere with compliance and lead to premature discontinuation of treatment (Niaspan PI 2013).

A new treatment for patients with high TG (200 to 499 mg/dL) that can safely and

effectively be added on to a statin to lower TG, VLDL-C, LDL-C, Apo B, Lp-PLA₂, and non-HDL-C is needed.

Vascepa has been shown to be a safe and effective therapy when added to statin therapy to significantly reduce TG, while meeting the FDA-agreed pre-specified non-inferiority assessment for LDL-C. In ANCHOR, the placebo adjusted change in fasting TG from baseline at Week 12 with Vascepa 4 g/day was -21.5 percentage points ($p < 0.0001$). Improvements in other lipid and inflammatory parameters were also demonstrated, including non-HDL-C, LDL-C, VLDL-C, RLP-C, Apo B, Lp-PLA₂, hsCRP, ox-LDL, RLP-C, and LDL-P concentration and size. These results suggest a beneficial effect on a fuller picture of atherogenic risk, including lipid burden and inflammation, both associated with plaque formation and atherosclerosis. The data support the conclusion that Vascepa provides benefits to patients when taken as an adjunct to diet and in combination with a statin for the reduction of TG, non-HDL-C, Lp-PLA₂, Apo B, LDL-C, TC, and VLDL-C in patients with mixed dyslipidemia and high risk for CVD.

Within the clinical studies, Vascepa was well tolerated with a low incidence of reported AEs. Overall, AE incidence was similar to placebo. There were no clinically meaningful changes in laboratory parameters. No statistically significant differences were seen in the efficacy or safety profile in diabetic patients compared to non-diabetic patients. Prior studies using omega acid mixtures have reported adverse events such as bleeding and hepatic disorders. These AEs were reviewed for Vascepa. Within the clinical program, Vascepa demonstrated no clinically meaningful effect on hepatic function. The incidence of bleeding-related AEs in ANCHOR was low in all treatment groups, but occurred more often on Vascepa (2.4%) than on placebo (1.3%). Even though the incidence is greater, it remains substantially low. Currently approved labeling for Vascepa advises physicians that omega-3s may be associated with an increased risk for bleeding. Since approval of the original NDA for severe hypertriglyceridemia, no new safety concerns have emerged.

Vascepa offers advantages over existing TG-lowering therapies. One of key benefits of Vascepa therapy is the absence of a significant increase of LDL-C, since fibrates and omega acid complex mixtures that contain EPA+DHA are known to increase LDL-C levels in hypertriglyceridemic patients (Goldberg 1989, Bays 2008). A further benefit of Vascepa therapy is that it does not interfere with glucose control. While small numerical elevations were seen in FPG, they were not statistically significant or clinically meaningful. The more accurate markers of glucose control (insulin, HbA1c, HOMA-IR) were similar between active and placebo arms.

Patients who are at high risk for CVD who are taking statin therapy and have persistently

high TGs are at-risk and need a safe and effective therapy that can be added to their statin therapy for more aggressive and comprehensive lipid control. If approved, Vascepa would fill an important unmet medical need for these patients.

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